Transition Metal Catalyzed Reactions for Forming Carbon–Oxygen and Carbon–Carbon Bonds

Sølvhøj, Amanda Birgitte

Publication date:
2015

Document Version
Publisher's PDF, also known as Version of record

Transition Metal Catalyzed Reactions for Forming Carbon–Oxygen and Carbon–Carbon Bonds

Amanda Birgitte Sølvhøj

Ph.D. Thesis

February 2014

DTU Chemistry
Department of Chemistry

Transition Metal Catalyzed Reactions for Forming Carbon–Oxygen and Carbon–Carbon Bonds

Amanda Birgitte Sølvhøj

Ph.D. Thesis

February 2014

"If we knew what we were doing,
it wouldn't be called research"

A. Einstein

Preface

This thesis describes the work performed during my three years as a Ph.D. student. During this time I have been working on three distinct projects, which at first glance may seem quite different, but which all share the same focal point, namely transition metal catalyzed reactions for forming C–O and C–C bonds, as indicated by the title. The thesis is divided into four chapters: One for each of the three projects, as well as an introduction which aims to emphasize why catalysis is such an important tool in addressing the challenges our society is facing today and outline where my own research is placed within this context.

The work described was performed at the Technical University of Denmark, under the supervision of professor Robert Madsen, from April 2010 to September 2011 (Chapter 2: "Dehydrogenative ester formation with a ruthenium NHC complex") and from January 2013 to January 2014 (Chapter 4: "Manganese catalyzed radical formation of styryl derivatives") and at the University of California Berkeley, under the supervision of professor Peter Vollhardt, from August to December 2012 (Chapter 3: "Synthesis of Anti Zigzag-[5]-phenylene").

Apart from describing the work I have performed this thesis also marks the end of my time as a Ph.D. student. It took blood, sweat and countless liters of heptane, but here I am - and it has been a very rewarding, instructive, interesting, industrious, fun and unforgettable time. I realize that while it felt that way sometimes, I was - fortunately - never alone, and some people must now be credited to give thanks where it is due.

First and foremost I would like to express my profound gratitude towards my supervisor professor Robert Madsen; for providing me with the opportunity to write a Ph.D. in his group and for all his good advice, support, trust and understanding along the way. It has been great, beyond expectations.

Thanks to the whole Madsen group, former and current members alike, you are all wonderful people and I have really enjoyed your company. In particular Camilla Arboe Jennum, Agnese Maggi and Ilya Makarov, who have been my lab-mates and office-mates and with whom I have shared many fun moments,

great discussions and grave worries along the way. Thanks to Esben Olsen for agreeing to proofread this little pamphlet, to Stig Holden Christensen for all the high-fives and to Andreas Ahlburg for entering the manganese project at a late stage with such great enthusiasm, synthesizing the substituted β-bromostyrenes in table 4.4 for me.

Also a very warm thanks to the technical staff in building 201: Anne Hector, Janne Borg Rasmussen, Tina Gustafsson, Brian Ekman-Gregersen, Brian Brylle Dideriksen, Patrick Scholer and Lars Egede Bruun – With you onboard it has been smooth sailing all the way and I know I will miss your help no matter where I'll go from here. Thanks to my dear friends of the former lunch club: Camilla, Agnese, Kennedy Taveras and Gyorgyi Osztrovszky - you rock!

And last but not least thanks to everybody else in building 201 at DTU – So long, and thanks for all the fish.

Thanks to professor Peter Vollhardt for giving me the chance to work in his group at UC Berkeley during my external stay. That was a great and rewarding experience, both professionally and personally, and I am very grateful that I got the opportunity. I would also like to thank the rest of the Vollhardt group: Bonnie Kirk, Dr. Zongrui Hou (Ray), Ziyan Feng and Dr. Jingqi Guan. I am happy I got to know you all. Also thanks to Henrik Munch for the great lunch company at UCB.

I am grateful to Knud Højgaards Fond, Otto Mønsted Fonden, Oticon Fondet, Augustinus Fonden, the Danish Chemical Society and the Technical University of Denmark (DTU) for supporting my external stay financially. Without your gold it would not have been possible.

Finally, thanks to all my friends for still being my friends even though I have been buried in chemistry and for making sure that I get out once in a while. A special thanks goes to Michel Winckler-Krog for providing me with graphical assistance for the front page.

I am grateful to my family – biological as well as in-laws and in-spirits – for their nearly inexhaustible patience, love and support. To my parents for providing me with such a strong foundation, to good old Moffe for always being proud of me, to my husband Jakob for always making me laugh and to my son Birk – you are the light of my life.

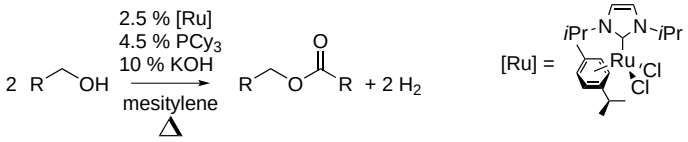
February, 2014 – Amanda

Abstract

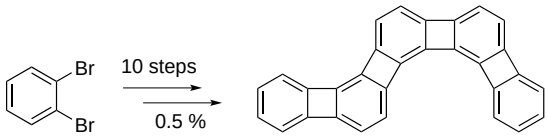
Dehydrogenative ester formation with a ruthenium NHC complex
A new atom-economical methodology for synthesizing esters by the dehydrogenative coupling of primary alcohols was developed. The reaction is catalyzed by the ruthenium N-heterocyclic carbene complex $RuCl_2(I^iPr)(p\text{-cymene})$. By screening the effect of different additives, solvents and loadings on the selfcondensation of pentanol, the optimal reaction conditions were found to be 2.5 mol % of $RuCl_2(I^iPr)(p\text{-cymene})$, 4.5 mol % of PCy_3 and 10 mol % of KOH in refluxing mesitylene, which gave the ester in nearly quantitative yield by GC analysis.

The substrate scope was shown to include a range of different straight-chain and branched primary aliphatic alcohols, which reacted to give the corresponding esters in moderate to excellent yields. Condensation of diols also proceeded well, giving the corresponding lactones in good yields. Benzylic alcohols could be used as substrates, but the yields were generally poor due to decarbonylation of the substrate as a considerable side reaction.

Some preliminary mechanistic investigations were performed. The results of these confirmed that the reaction is indeed dehydrogenative with the liberation of two moles of hydrogen per formed mol of ester as assumed. Furthermore a disproportionation mechanism (Tishchenko) could be ruled out due to the fact that free aldehydes did not enter the catalytic cycle. Fast deuterium/hydrogen exchange in the reaction with benzyl alcohol points towards a ruthenium dihydride species being the catalytically active species. A catalytic cycle consistent with these findings, as well as with previous knowledge about this particular catalytic system, was proposed.

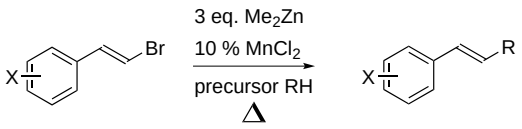


Synthesis of Anti Zigzag-[5]-phenylene A new member of the family of [5]-phenylenes, named Anti Zigzag-[5]-phenylene, was synthesized and characterized. The desired target molecule was synthesized in ten steps from the commercially available starting material 1,2-dibromobenzene in an overall yield of 0.5 %. Six of the ten steps had not been performed before and six new compounds were isolated and characterized in the process. The target molecule was characterized by HRMS and proton NMR.



Manganese catalyzed radical formation of styryl derivatives A new method for the formation of styryl derivatives by the reaction of ether and hydrocarbon radicals with β-bromostyrenes was serendipitously discovered and subsequently optimized. By screening of various radical initiators and transition metal salts the best conditions were found to involve addition of three to four equivalents of Me_2Zn to a solution of β-bromostyrene, using the radical precursor as solvent, in the presence of 10–12 % of $MnCl_2$, and refluxing overnight in the presence of air. A simple acidic workup and purification by chromatography yielded the products in moderate to good yield.

The radical precursor can be a cyclic or acyclic ether or even a cycloalkane, although the latter gives only poor conversion. The β-bromostyrene can be substituted with electrondonating or electronwithdrawing substituents in the para position without affecting the yield of the reaction remarkably. The reaction is quenched when TEMPO is added, which confirms that the reaction occurs by a radical mechanism. The reaction is believed to be initiated by the formation of a methyl radical from the reaction of Me_2Zn with oxygen. The methyl radical abstracts a hydrogen from the radical precursor and the resulting radical then adds to the β-bromostyrene, which subsequently eliminates a bromo radical and forms the product.

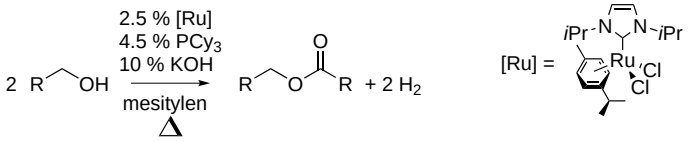


Resumé

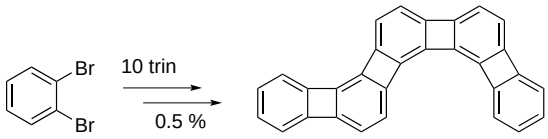
Dehydrogenativ dannelse af estere med et ruthenium NHC kompleks
En ny atom-økonomisk metode til at fremstille estere ved en dehydrogenativ kobling af primære alkoholer er blevet udviklet. Reaktionen er katalyseret af et ruthenium N-heterocyklisk carben kompleks, $RuCl_2(I^iPr)(p\text{-cymene})$. Ved at undersøge effekten af forskellige ligander, baser, solventer og stofmængder er det blevet fundet, at de optimale reaktionsbetingelser er med 2.5 mol % $RuCl_2(I^iPr)(p\text{-cymene})$, 4.5 mol % PCy_3 og 10 mol % KOH i refluksende mesitylen, hvilket giver esteren i nær ved kvantitativt udbytte, ifølge GC analyse.

Omfanget af substrater der kan anvendes inkluderer et udvalg af forskellige ligekædede og forgrenede primære alifatiske alkoholer, som reagerer under dannelse af de tilsvarende estere i moderat til glimrende udbytte. Kondensering af dioler forløber også tilfredsstillende og giver de tilsvarende laktoner i godt udbytte. Benzyliske alkoholer kan også anvendes som substrater, men udbyttet er generelt ringe, hvilket antages primært at skyldes at decarbonylering er en væsentlig sidereaktion.

Nogle indledende mekanistiske undersøgelser er blevet udført. Resultaterne fra disse bekræfter at reaktionen er dehydrogenativ, med frigivelse af to mol hydrogen gas per mol ester dannet, som antaget. Ydermere kan en disproportionerings mekanisme (Tishchenko) udelukkes, da det ikke er muligt for frie aldehyder at indgå direkte i den katalytiske cyklus. Hurtig udskiftning af deuterium og hydrogen i reaktionen med benzyl alkohol indikerer at et ruthenium dihydrid er den katalytisk aktive forbindelse. En katalytisk cyklus som stemmer overens med disse resultater, og som også er konsistent med tidligere opnået viden om netop dette katalytiske system, er blevet fremsat.

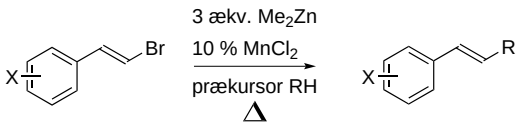


Syntese af Anti Zigzag-[5]-phenylen Et nyt medlem af [5]-phenylen familien, kaldet Anti Zigzag-[5]-phenylen, blev fremstillet og karakteriseret. Det ønskede målmolekyle blev syntetiseret i ti trin fra det kommercielt tilgængelige udgangsstof 1,2-dibrombenzen i et overordnet udbytte på 0.5 %. Seks af de ti trin havde ikke tidligere været udført og seks nye forbindelser blev isoleret og karakteriseret i processen. Målmolekylet blev karakteriseret ved hjælp af HRMS og proton NMR.



Mangan katalyseret radikal dannelse of styryl derivater En ny metode til dannelse af styryl derivater ved reaktionen mellem æter- og kulhydrat radikaler og β-bromstyrener blev opdaget ved et tilfælde og efterfølgende optimeret. Ved at undersøge effekten af forskellige radikal initiatorer og overgangsmetal salte blev de bedste reaktions betingelser fundet. Disse involverer tilsætning af tre ækvivalenter Me_2Zn til en opløsning af β-bromstyren under tilstedeværelse af 10–12 % $MnCl_2$. Prækursoren til det ønskede radikal anvendes som solvent og reaktionsblandingen reflukser natten over under tilstedeværelse af ilt. En simpel vandig oprensning og kromatografisk oprensning giver produktet i moderat til godt udbytte.

Den radikale prækursor kan være en cyklisk eller acyklisk æter eller sågar en cykloalkan, omend sidstnævnte giver meget ringe omdannelse. β-Bromstyrenen kan substitueres i para-positionen med elektrondonerende eller elektrontiltrækkende substituenter uden at udbyttet påvirkes nævneværdigt. Reaktionen inhiberes ved tilsættelse af TEMPO, hvilket bekræfter formodningen om at reaktionen forløber via en radikal mekanisme. Reaktionen menes initieret ved dannelsen af et methyl radikal fra reaktionen mellem Me_2Zn og ilt. Methyl radikalet abstraherer et hydrogen fra den radikale prækursor og det herved dannede radikal adderer til β-bromstyren, som efterfølgende eliminerer et brom radikal under dannelse af produktet.



Contents

CHAPTER 1

Introduction to catalysis

This introduction aims to emphasize the importance of catalysis as a tool for addressing some of the challenges our society is facing today. It provides a short presentation of the most fundamental concepts of catalysis as well as a brief historic overview, from the first use of the term catalysis to some of the most recent advances in the field. Finally it outlines where the research presented in this thesis belongs in this context.

1.1 Fundamental principles

According to IUPAC's definition of terms 'Catalysis' is the action of a catalyst. A catalyst is defined as a substance which increases the reaction rate without changing the overall standard Gibbs energy of the reaction; in other words by lowering the activation energy of the rate-determining step.[1] This may be done in two different ways: Either by stabilizing the intermediate but otherwise follow the same mechanism as for the uncatalyzed reaction or by changing the reaction mechanism so the energy profile of the catalyzed and uncatalyzed reactions are completely different. The former is typically the case for enzymatic reactions, while the latter, shown schematically in figure 1.1, typically is the case for catalysis with transition metal complexes.

The reactants and products of the reaction are still the same, but the mechanism and intermediates have changed so that less energy is required for the transition state(s) to be reached. In theory the reaction would also occur un-

catalyzed, since it is energetically favorable, but in practice it may be infinitely slow or require such a high temperature that the substrate would decompose before being transformed. The diminished energy requirement either increases the reaction rate at the applied temperature or allows for the reaction to run at a lower temperature.

Since the catalyst partakes in the reaction without being consumed it only needs to be present in sub-stoichiometric amounts, also known as catalytic amounts. In principle one single molecule of the catalyst should be enough, but in practice most catalysts lose their potency after a certain number of turn-overs, called the turn-over number (TON) of the catalyst. The TON is also called the productivity of the catalyst and the higher productivity a catalyst has, the lower catalyst loading is necessary. Closely related to the productivity of a catalyst is its activity, also known as the turn-over frequency (TOF) which is the TON per time unit.

The mechanism of a single turn-over is known as the catalytic cycle of the reaction. The catalytic cycle describes in detail how a single molecule of the catalyst is changed during the course of the reaction, regarding for example the oxidation state of a metal center, which ligands are bound to it and their mode of binding, like for example π– or σ–bonds. The catalytic cycle commences with the complexation of the substrate and ends with the release of the product, thereby regenerating the active catalyst. The catalytic cycle is not necessarily a detailed mechanism for the full reaction, but rather is concerned only with what occurs on the catalyst.

Catalysis can broadly speaking be divided into two main areas: Heterogeneous and homogeneous catalysis. As the term implies heterogeneous catalysis involves a catalyst in another physical state than the substrates. This could

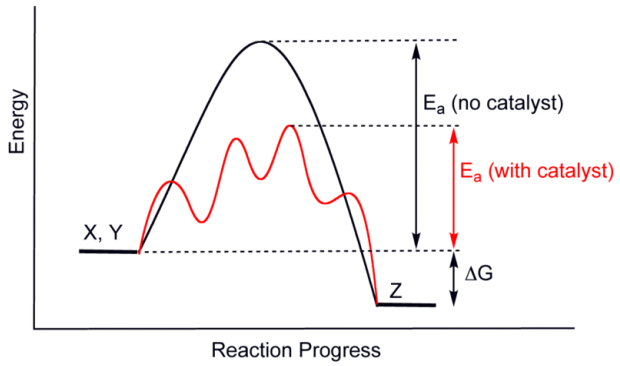


Figure 1.1: A catalyst works by changing the mechanism and transition states of the reaction, such that the activation energy of the reaction is lowered.

for example be a solid which is insoluble in the solution where the reaction occurs and where the catalytic process takes place at the surface of the solid. With homogeneous catalysis the catalyst and substrates are in the same phase, typically in solution. Enzymatic catalysis, which is the action of enzymes on substrates, is usually homogeneous, but is most often treated in a category by itself.

The obvious benefits of catalytic reactions, compared to regular chemical transformations, are the use of very small amounts of reagents (catalytic amounts), the relatively low energy requirements and the possibility of performing reactions, which would otherwise not be possible, in an efficient way. As will be elaborated in the following section these features makes catalysis an indispensable tool for addressing some of the challenges society is facing today, by improving already existing chemical reactions as well as for developing new efficient synthetic methods.

1.2 A historic perspective

Catalysis has been applied by mankind for countless millennia, as the use of yeast for fermentation in brewing is a catalytic process. Back then of course it did not have a name; the definition of catalysis, and thereby the science of catalysis, was not born until the beginning of the 19th century.

Since then it has been continuously evolving and the understanding of the principles behind the processes has improved steadily with the development of new theories, new tools for analysis and by the consideration of the ever expanding set of experimental data. The increased understanding led to the development of more catalytic processes and the efforts to apply these newly developed processes to solve the societal challenges of the time resulted in even more experimental data being collected – and so it continues.

Today we have a vast array of catalytic processes at our disposal and our understanding of catalysis has never been better. At the same time the challenges we face as a society is more pressing and severe than ever before: We are facing climate changes, rapidly dwindling natural resources and an exponentially growing world population demanding the same levels of commodities as those which are available to the inhabitants of the western world. This means an increasing demand for renewable energy and more efficient and environmentally benign processes for the production of chemical compounds, ideally utilizing otherwise useless biomass leftovers as starting materials. To address all these problems the development, understanding and application of new catalytic reactions are more relevant than ever.

1.2.1 A short history of catalysis

The term catalysis was first coined by the Swedish chemist Berzelius in 1835. Before then many catalytic processes had been observed by other chemists, but not explained or recognized for what they were. Berzelius performed a systematic investigation of these phenomenon and presented the definition of catalysis as the ability of some chemical compounds to cause a transformation of reactants, which would otherwise not occur, without being consumed in the process itself.[2]

Berzelius' definition of catalysis was modified by Ostwald in 1885, who had discovered that reactions happen with a certain rate, which he called the velocity of the reaction. He claimed that catalysts are substances which change the velocity of the reaction without modification of the energy factors of the reaction, which is very similar to the currently accepted definition. Ostwald was awarded the Nobel Prize in chemistry in 1909 for his work on catalysis.[3]

Up through the 20th century the field of catalysis, like many other areas of chemistry, experienced an explosive growth. History shows an undeniable connection between the current political and societal issues of a certain era and the development of new technologies at the time and the field of catalysis is no exception. The first half of the 20th century faced an extensive industrialization, two world wars and a rapidly growing automobile industry. This is mirrored in the achievements of the field of catalysis of that time, which include industrial processes for the production of chemicals, catalysts for the cracking of hydrocarbons and for the production of kerosene, alkylates and synthetic rubber.[4]

One of the most important milestones is Habers process for the production of ammonia from nitrogen and hydrogen (figure 1.2). Haber discovered the process in 1909 and five years later Bosch developed an industrial scale implementation of the method. Haber was awarded the Nobel Prize for his discovery in 1918 and Bosch received the same honor together with Bergius in 1931, for their contributions to the invention and development of chemical high-pressure methods. Another significant discovery is the Fischer-Tropsch process (1926)

(1) $N_2 + 3\,H_2 \longrightarrow 2\,NH_3$

(2) $(2n+1)\,H_2 + n\,CO \longrightarrow C_nH_{2n+2} + n\,H_2O$

Figure 1.2: (1) The Haber process. The reaction is performed at high pressure and elevated temperatures, typically 15–25 MPa and 300–550 °C, in the presence of an iron catalyst. (2) The Fischer-Tropsch process. The reaction is typically performed at a temperature range of 150–300 °C, at high pressure, in the presence of a transition metal catalyst like cobalt, iron or ruthenium.

for the production of hydrocarbons from carbon monoxide and hydrogen (figure 1.2). Both methods are still widely applied on an industrial scale today.

Up through the 50's and 60's the field of catalysis evolved rapidly and a myriad of new inventions and theories saw the light of day. The importance of catalysis as a field of research in its own right was solidified by the conferences and journals devoted solely to catalysis which appeared in those years: The first conference for heterogeneous catalysis was organized by the Faraday Society in 1950, the first International Conference on Catalysis (ICC) was held in 1956 and the Journal of Catalysis was published for the first time in 1962. Among the many new catalytic systems developed in this period the polymerization catalysts are probably the most significant. Most famously the discovery of a catalytic system for the polymerization of ethylene by Ziegler in 1953 and the stereospecific polymerization of propylene by Natta in 1954, both of whom received the 1963 Nobel Prize for their work.[5]

The energy crisis of the 1970's laid the foundation for research in the formation of gasoline and chemicals from other raw materials than oil. It also brought about an increased awareness of the environment, which grew steadily through the last decades of the 20th century, leading to the development of catalysts for the cleansing of exhaust gas and for the improvement of chemical synthesis, thereby reducing the amount of chemical waste as one of the benefits.[4]

The area of palladium catalyzed cross-coupling reactions, which has later grown to be of immense importance to the field of organic chemistry, was founded in the 70's.[6] The first papers on the palladium catalyzed coupling of alkenes with aryl-halides were presented by Mizoroki in 1971 and by Heck in 1972,[7] the coupling of terminal alkynes with aryl-halides by Sonogashira in 1975,[8] the coupling of alkynylzinc reagents with alkenylhalides by Negishi in 1977,[9] the coupling of aryl and acyl halides with organotin reagents by Stille and others in the years 1975 to 1978[10] and finally the coupling of boronic acids with aryl halides by Suzuki in 1979.[11] Over 30 years later Heck, Suzuki and Negishi were awarded the 2010 Nobel Prize for their contributions – by then palladium catalyzed reactions had become one of the most utilized and versatile ways of forming C-C bonds in organic chemistry and this type of reaction alone accounted for 10 % of the reactions performed in the pharmaceutical industry in 2010.[12]

The 1990's saw the birth of the concept "green chemistry" – an area of research which emerged from a combination of the scientific discoveries about pollution of the environment and the public demand to do something about it, once the consequences of these discoveries became general public knowledge. The green chemistry strives to replace chemical processes which carry a negative impact on the environment with less polluting alternatives.[13] Catalysis is viewed as one of the most important tools to achieve the goals of green chemistry, as

the design of catalysts strives to enhance the efficiency of a reaction, thereby minimizing the amount of waste produced or even allowing for the use of more environmentally friendly feedstocks and reagents.[14]

Now at the beginning of the 21st century the ongoing climate changes are high on the political agenda and thus ample incentives are provided to do research with focus on sustainable energy. Within the field of catalysis this means catalysts for the transformation of biomass into fuels and chemicals, electrocatalysts for fuel cells and photocatalysis to utilize the energy of the sun.[4]

In addition to the agendas outlined above there is also a general demand by various industries for the development of new and more efficient synthetic methods, and catalysis is a very important tool in this regard. For the pharmaceutical industry the development of new synthetic methods is of paramount importance as it allows for the synthesis of new types of compounds, potentially leading to the discovery of new effective drugs. The development of new and more efficient ways to synthesize known compounds lowers the cost of production, which is a benefit for all types of industry which involve chemical synthesis or the use of synthetically manufactured chemicals – and it reduces the negative impact on the environment, which is a benefit for everyone.

1.2.2 Relevant topics of today

Dehydrogenative reactions Green chemistry, although founded 20 years ago, is still a relevant area of research. The development of synthetic methods which are more environmentally benign is a very desirable goal, and catalysis is one of the most promising ways to reach it. Green chemistry follows a set of 12 principles, one of them being that "Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product."[14] This principle is based on the concept of atom-economy first presented by Trost in 1991.[15] The best way to achieve good atom economy is of course by simple additions and rearrangements, where all of the atoms in the reactants are also present in the products. That is not always possible and this is when efficient catalytic reactions comes in play. An efficient catalyst only needs to be present in very small amounts and ideally requires no other additives or reagents; the perfect substrate is one where a large percentage of the original atoms stay where they are during the chemical transformation. With the fulfillment of both of these requirements a reaction would be highly atom-economical.

Dehydrogenative reactions are an example of the latter, namely utilization of substrates where the only redundant atoms are hydrogens which are cleaved off, producing molecular hydrogen as the only byproduct. The development and study of dehydrogenative reactions is a rapidly ascending field of research

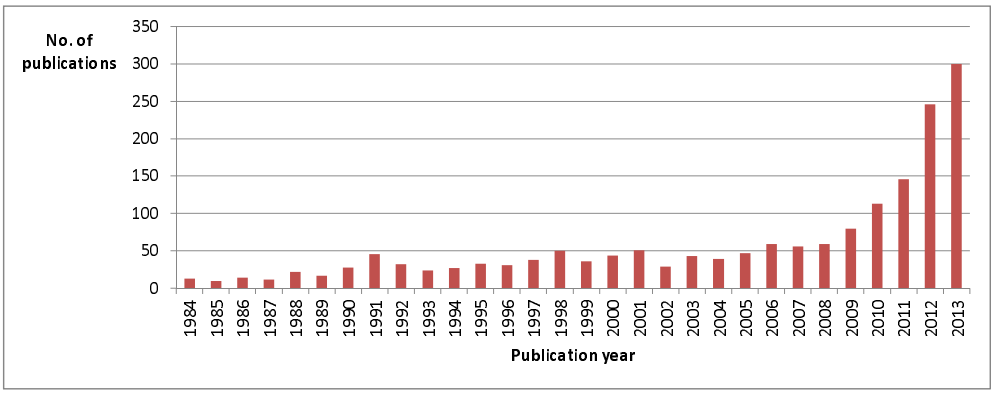


Figure 1.3: The number of publications about dehydrogenative reactions each year for the last 30 years. Source: Scifinder.

within the area of catalysis: A search on scifinder reveals that the number of papers published each year which contains the word dehydrogenative has increased explosively within the last five years, shown graphically in figure 1.3. In chapter 2 of this thesis the development of a new atom-economical way of synthesizing esters by the dehydrogenative coupling of primary alcohols, catalyzed by a ruthenium NHC complex, is presented. The method, although still in its infancy, provides a new way to synthesize esters, which is a compound class that is produced industrially on a very large scale every year. In the long run, the implementation of such methods will help to decrease the negative impact that chemical industry imparts on the environment.

Manganese catalyzed cross coupling reactions Another area of catalysis which has received a lot of attention in the recent years is the attempt to perform cross coupling reactions with other metals than palladium, like iron,[16] copper[17] and cobalt.[18] As was mentioned in the historical overview the palladium catalyzed cross coupling reactions has had a tremendous impact on organic chemistry,[6] and thereby on the many areas of industry applying organic synthesis. Unfortunately there is a downside and palladium has some serious drawbacks. These include low availability which makes the use of palladium expensive and the high toxicity of the metal which is a big concern, not least to the pharmaceutical industry. The utilization of cheaper, less toxic and more environmentally benign metals to perform the same transformations is highly desirable from both an economical and environmental point of view.

The substitution of palladium for manganese as catalyst in these types of reactions would be highly desirable, as manganese is both cheap, abundant and not particularly toxic. Furthermore the field of manganese chemistry is rela-

tively unexplored compared to that of other transition metals. This goal was the starting point for the project described in chapter 4 of this thesis. Although the preliminary attempts described here did not immediately result in the development of the desired manganese catalyzed cross coupling reactions, they still provide valuable information regarding a field of research of immense relevance today. Furthermore, these preliminary experiments led to the serendipitous discovery of a new manganese catalyzed radical reaction, which may prove to be a valuable synthetic tool in its own right.

Practical applications of transition metal catalyzed reactions Finally, it must be mentioned that while many efforts are made to apply catalysis to solve some of the great societal challenges of the present time, like the pollution of our environment or the need for sustainable energy, they are also indispensable tools for solving challenges in the world of chemistry. Often the total synthesis of a desired compound, like a natural product or a molecule of particular theoretical or practical interest, would not be possible without the application of a certain catalytic method. The practical applications of catalytic reactions in organic synthesis is still a topic of immense interest and probably will remain so as long as organic synthesis exists as an academic discipline.

Chapter 3 of this thesis describes the synthesis of the PAH anti-zigzag-[5]-phenylene, which is a molecule of primarily theoretical interest. The synthesis is accomplished by the application of three palladium catalyzed cross coupling reactions and a cobalt catalyzed cyclization and in this way shows the unrivaled synthetic capacities that can be achieved by the practical applications of transition metal catalyzed reactions.

CHAPTER 2

Dehydrogenative ester formation with a ruthenium NHC complex

This chapter describes the development of a new atom economical method for the synthesis of symmetric esters and lactones by the dehydrogenative self-coupling of primary alcohols and diols, respectively. The reaction is catalyzed by a ruthenium N-heterocyclic carbene (NHC) complex and by investigation of the effect of different additives on the coupling of two pentanol molecules to form pentyl pentanoate, the optimal conditions for this model system was found to be a combination of $RuCl_2(I^iPr)$(p-cymene) (2.5 mol %), KOH (10 mol %) and PCy_3 (4.5 mol %) in refluxing mesitylene, which provided the product in nearly quantitative yield by GC analysis. The substrate scope included various straight chain and branched alkyl alcohols as well as diols and benzylic alcohols, with yields ranging from excellent to poor. The mechanism was investigated and a catalytic cycle proposed.

2.1 Introduction

In the recent years a lot of effort has been directed into decreasing the negative influence that the chemical industry imparts on the environment. Green chemistry is defined as "the design of chemical products and processes to reduce or eliminate the use and generation of hazardous substances".[19] Reactions where the amount of waste and byproducts is reduced are referred to as "atom economical".[15] This means that the reaction involves no redundant atoms which would

only end up as useless waste after the reaction has run its course. Few chemical transformations exist, apart from rearrangements or additions over multiple bonds, where new products are formed from reactants without any byproducts accompanying the process. However, reactions like dehydrogenations where the only byproducts are small molecules like H_2 and water must be considered very atom-economical indeed, and therefore new dehydrogenative reaction protocols are very desirable from a chemical as well as an environmental point of view.

The field of catalytic dehydrogenative reactions is in rapid development and the last decade has seen a striking increase in new catalysts based on different transition metals able to perform a large variety of dehydrogenative reactions.[20] The attention that this kind of chemistry receives really emphasizes the importance of finding new and more environmentally benign ways of performing classic chemical transformations that are still used widely in the chemical industry.[21] A comprehensive review on all of these catalysts and transformations would be far beyond the scope of this thesis to describe and therefore the current introduction is limited to the description of a few dehydrogenative reactions, namely amidations, iminations and esterifications, and in particular the use of the $RuCl_2(I^iPr)(p\text{-cymene})$ complex to perform these reactions.

2.1.1 Dehydrogenative amidation reactions

In 2007 Milstein and coworkers discovered a ruthenium catalyzed formation of amides from primary alcohols and amines by the extrusion of hydrogen.[22] It was well known at the time that certain ruthenium and iridium complexes catalyze the alkylation of amines with alcohols,[23] presumably through an imine intermediate, but the exclusive formation of the amide was unique and had only previously been reported as an intramolecular lactamization of aminoalcohols by Naota and coworkers in 1991.[24] The catalyst presented in Milsteins paper was a ruthenium PNN pincer complex, shown in figure 2.1, and the reaction was conducted in refluxing toluene under a flow of inert gas with only 0.1 mol % of the catalyst. The substrate scope was limited to aliphatic primary alcohols and a selection of a few primary and secondary amines, but the yields in general were good, and the reaction proceeded without addition of any promoters, hydrogen scavengers or other additives. The largest disadvantage of this system at the

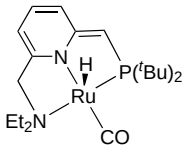


Figure 2.1: The ruthenium PNN pincer complex used by Milstein and coworkers.

time of its publication was the fact that the utilized catalyst was only available through a rather tedious synthesis.[25] Still the reaction was selected as one of the top ten breakthroughs in 2007 by the Science magazine, and this exposure probably laid the foundation for the subsequent availability of the catalyst from commercial suppliers under the trade name "Milstein Catalyst".

The following year Madsen and coworkers reported a new catalytic system to facilitate the same transformation, which consisted of the commercially available ruthenium complex $Ru(COD)Cl_2$, in the presence of a NHC ligand, a phosphine and a base.[26] The optimal reaction conditions were found to be in refluxing toluene, with $Ru(COD)Cl_2$ (5 mol %), 1,3-diisopropyl imidazolium chloride (I*i*PrCl, 5 mol %), potassium *tert*-butoxide (20 mol %) and tricyclopentyl phosphine (5 mol %) in the form of the more stable tetrafluoroborate salt. The substrate scope mainly consisted of benzylalcohol and 2-phenylethanol coupled with benzyl- and hexylamine, along with some variations, including the intramolecular reaction of 4-aminobutan-1-ol to give gammabutyrolactam. Chiral alcohols employed in the reaction retained their stereochemistry. The yields were moderate to excellent depending on the substrates, with the best combination being the coupling of 2-phenylethanol with hexylamine affording *N*-hexyl-2-phenylacetamide in quantitative yield.

A comprehensive study of the reaction was published by the Madsen group two years later.[27] The compound $RuCl_2(I^iPr)(p\text{-cymene})$ was synthesized and employed in the same reactions in the presence of a phosphine ligand and a base. Since compounds of this type is known to lose the *p*-cymene ligand at temperatures above 85 °C,[28] $RuCl_2(I^iPr)(p\text{-cymene})$ is actually a Ru(II)chloride NHC complex under the applied conditions. Furthermore, the Hoveyda-Grubbs 1. generation metathesis catalyst was tested, also in the presence of a NHC ligand and KO*t*Bu. The three catalytic systems are shown in figure 2.2. All three systems showed similar reactivity, although the preformed $RuCl_2(I^iPr)(p\text{-cymene})$ complex in general gave slightly higher yields. These findings support the theory that the active catalyst for all three of them is the same Ru(II)chloride NHC complex. The scope of the reaction was expanded further to include aliphatic

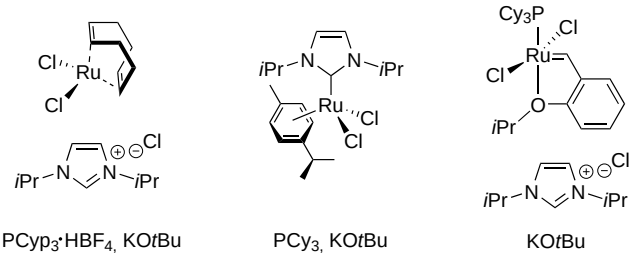


Figure 2.2: The three different catalytic systems tested by Madsen and coworkers.

alcohols and chiral amines as substrates.

Simultaneously and subsequently several other catalytic systems based on ruthenium as well as rhodium, silver and rhenium has been published. An almost identical ruthenium-based catalytic system has been reported in numerous variations by the research group of Hong: Without phosphines present,[29] with $RuCl_3$ in the presence of a NHC ligand, a phosphine and a base[30] and with $RuH_2(PPh_3)_4$ or $RuH_2(CO)(PPh_3)_3$ in the presence of a NHC ligand, a phosphine and a base,[31] just to mention a few. Williams and coworkers reported the use of $[Ru(p\text{-cymene})Cl_2]_2$ in combination with dppb, Cs_2CO_3 and 3-methyl-2-butanone as hydrogen acceptor for the direct synthesis of secondary amides from primary alcohols and amines.[32] A rhodium-based catalytic system to facilitate the dehydrogenative coupling of primary alcohols with water, methanol or amines to form carboxylic acids, methyl ester and amides respectively, was reported by Grützmacher and coworkers.[33] Shimizu and coworkers presented a γ-alumina supported silver cluster that catalyzes the dehydrogenative formation of amides from amines and alcohols.[34] Klankermayer and coworkers reported the use of a rhenium-triphos complex as catalyst for the dehydrogenative formation of esters and amides from the coupling of primary alcohols with an alcohol or an amine respectively.[35] For a comprehensive description of these and other catalytic systems, several reviews exist.[20]

2.1.2 Dehydrogenative formation of imines

During the work on the $RuCl_2(I^iPr)(p\text{-cymene})$ catalyzed formation of amides from alcohols and amines it was found that by omitting the base the reaction gave imines as the main product instead. An independent experimental study was performed by the Madsen group and the results were published in 2012.[36] An extensive screening of different conditions on a model system consisting of benzyl alcohol and *tert*-octylamine was performed, and showed that the optimal reaction conditions were refluxing toluene, with 5 mol % of $RuCl_2(I^iPr)(p\text{-cymene})$, in the presence of 10 mol % of DABCO and 4Å molecular sieves, which resulted in formation of the imine in good yields, with only trace amounts of the secondary amine (from reduction of the imine) present. The reaction is shown in figure 2.3. Good yields were obtained with a variety of substituted

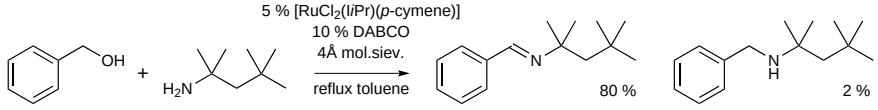


Figure 2.3: The optimized conditions for formation of imines from primary alcohols and amines with $RuCl_2(I^iPr)(p\text{-cymene})$.

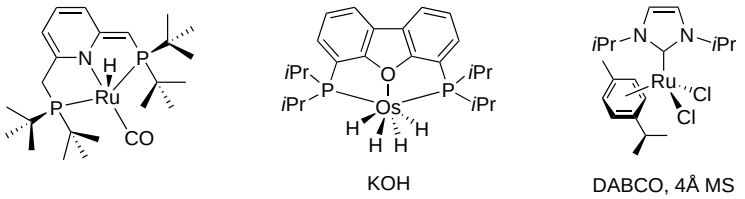


Figure 2.4: Catalytic systems for the dehydrogenative formation of imines from alcohols and amines. From left to right: a ruthenium PNN pincer complex, an osmium POP pincer complex and a ruthenium NHC complex.

benzyl alcohols and primary amines.

The direct formation of imines from the dehydrogenative coupling of alcohols and amines is a groundbreaking reaction that has only been reported with two other catalytic systems prior to the one described above. The first one was a ruthenium PNP pincer complex presented by Milstein and coworkers in 2010.[37] That complex is very similar to the ruthenium PNN pincer complex used for the formation of amides, but has a phosphine ligand instead of the amino ligand on the original complex, which alters the outcome of the reaction such that imines are the major observed product with only traces of the amide detected. Another catalytic system based on an osmium POP pincer complex have been presented by Esteruelas and coworkers in 2011.[38] This complex catalyzes the formation of imines from a rather broad range of alcohols and amines in good to excellent yields. Both catalytic systems, along with the one presented by the Madsen group in 2012, are shown in figure 2.4.

2.1.3 The catalytic cycle of $RuCl_2(I^iPr)(p\text{-cymene})$

The reaction mechanism of the $RuCl_2(I^iPr)(p\text{-cymene})$ catalytic system has been extensively studied, initially in the full paper on the amidation reaction from 2010[27] and recently a catalytic cycle has been proposed based on data from computational studies, deuterium labelling experiments, NMR- and Hammett studies.[39] These studies are also supported by mechanistic studies from the imination reaction[36] and the esterification reaction.[40]

Research from the 2010 paper showed that neither free esters, imines nor aldehydes were present as reaction intermediates, as subjecting these compounds to the general reaction conditions resulted in no reaction at all. The reaction is assumed to proceed through an aldehyde intermediate, but if this is the case the aldehyde must stay coordinated to the ruthenium complex and undergo further reaction from here. This was confirmed by performing a crossover experiment: Reacting a mixture of *p*-methylbenzyl alcohol and benzaldehyde with hexylamine under standard reaction conditions (figure 2.5) did not result in the

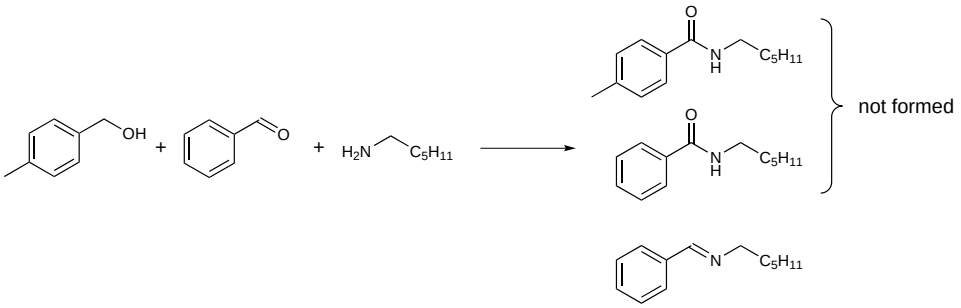


Figure 2.5: Reacting a mixture of *p*-methylbenzyl alcohol and benzaldehyde with hexylamine under standard reaction conditions did not result in the formation of *N*-hexylbenzylamide, showing that free aldehydes cannot enter the catalytic cycle.

formation of *N*-hexylbenzylamide, as would be the case if free aldehydes could enter the catalytic cycle, nor did the formation of *N*-hexyl-*p*-methylbenzylamide occur, as would be the expected product. Instead the aldehyde and the amine immediately reacted to form the imine, thereby inhibiting the formation of the amide from amine and alcohol. Slow addition of benzaldehyde to a reaction between *p*-methylbenzyl alcohol and hexylamine allows the formation of *N*-hexyl-*p*-methylbenzylamide to proceed as usual, but accompanied by the formation of the imine, further consolidating the theory.[27]

This theory is further supported by the results of a mechanistic investigation of the $[Cp^*IrCl_2]_2$ catalyzed alkylation of amines with alcohols published by Fristrup, Tursky and Madsen in 2012.[41] The proposed mechanism for this reaction can be summarized in three steps: Hydride transfer from the alcohol to iridium under formation of an aldehyde, formation of an imine from the aldehyde and the amine with release of water and finally a hydride transfer from iridium to the imine, regenerating the active catalyst and releasing the alkylated amine product. Based on computational as well as experimental data the authors concluded that both the aldehyde and the imine intermediates were formed as well as consumed within the coordination sphere of the iridium catalyst. Among the experimental data supporting this conclusion were the facts that the release of the aldehyde from the catalyst is slow compared to the forward reaction and that a preformed imine could not be reduced directly under the standard experimental conditions. The same conclusion was also reached by Yamaguchi and coworkers in a similar study from 2008.[42]

In the mechanistic study from 2012 several deuterium labeling experiments were conducted. Scrambling of deuterium and hydrogen in the α position on the alcohol was observed when using a mixture of benzyl alcohol-α,α-d_2 and regular benzyl alcohol. Running the reaction in deuterated toluene resulted in no deuterium exchange, ruling out the possibility that the exchange takes place

between solvent and substrate. Reacting non-deuterated benzyl alcohol with $BnND_2$ also resulted in deuterium incorporation in the α position of benzyl alcohol. At equilibrium the ratio between H/D was 3/2, indicating that five protons are involved in the exchange: The two α protons on the benzyl alcohol, the hydroxy proton from the alcohol and the two N-H protons on the amine. Repeating the experiment with non-deuterated benzylamine and benzyl alcohol-α,α-d_2 resulted in the same equilibrium ratio between H and D, but the exchange was observed even before the amide formation, meaning that a reversible β-hydride elimination and a migratory insertion step involving the alcohol probably takes place at the beginning of the reaction. These results indicate that a ruthenium dihydride complex is involved in the catalytic cycle, which again suggests that the chloride ligands on the precatalyst $RuCl_2(I^iPr)$(*p*-cymene) are not present on the active catalytic species. This statement is supported by the fact that exchanging the chloride ligands on $RuCl_2(I^iPr)$(*p*-cymene) for iodide does not affect the initial rate of the catalyzed reaction to any notable extent, although the yields do vary, possibly due to the reduced stability of the iodide complex.[39]

By NMR spectroscopy it was shown that the *p*-cymene ligand, as suspected, did not stay coordinated to ruthenium during the reaction. NMR experiments also revealed that several hydride species are formed during the reaction. More than one ruthenium-hydride complex where a phosphine is located cis to the hydride exists, as well as a dihydride species that does not contain a phosphine group. Hammett studies showed that no radicals were involved in the reaction, and that a small positive charge build up on the benzylic position in the turnover limiting step. A kinetic isotope effect (KIE) study showed that the breakage of the C-H bond is not the rate limiting step, but rather is one of several slow steps in the catalytic cycle.[39]

DFT calculations were performed on a simplified system reacting ethylamine with benzyl alcohol. The results of these calculations implied that one molecule of amine is coordinated to ruthenium throughout the reaction, and that likely a phosphine is occupying the apical position of the involved complexes.[39] It is known from similar ruthenium(II)-dichloride complexes that alcohols may displace the chloride ligands for an alkoxy- and a hydride ligand.[43] Since this was also supported by the experimental evidence described above, the complex **2** in figure 2.6 was proposed as the starting point for the catalytic cycle.

The catalytic cycle commences with the thermally induced loss of the *p*-cymene ligand from the 18 e^- complex **1**, rendering the metal center coordinatively unsaturated (12 e^-) and thus ready to coordinate one amine and one phosphine molecule. A molecule of alcohol displaces the chloride ligands for an alkoxy- and a hydride ligand to give the 16 e^- complex **2**. β-Hydride elimination from the alkoxide to ruthenium under the formation of a coordinated aldehyde gives the coordinatively saturated 18 e^- complex **3**, which is then attacked at

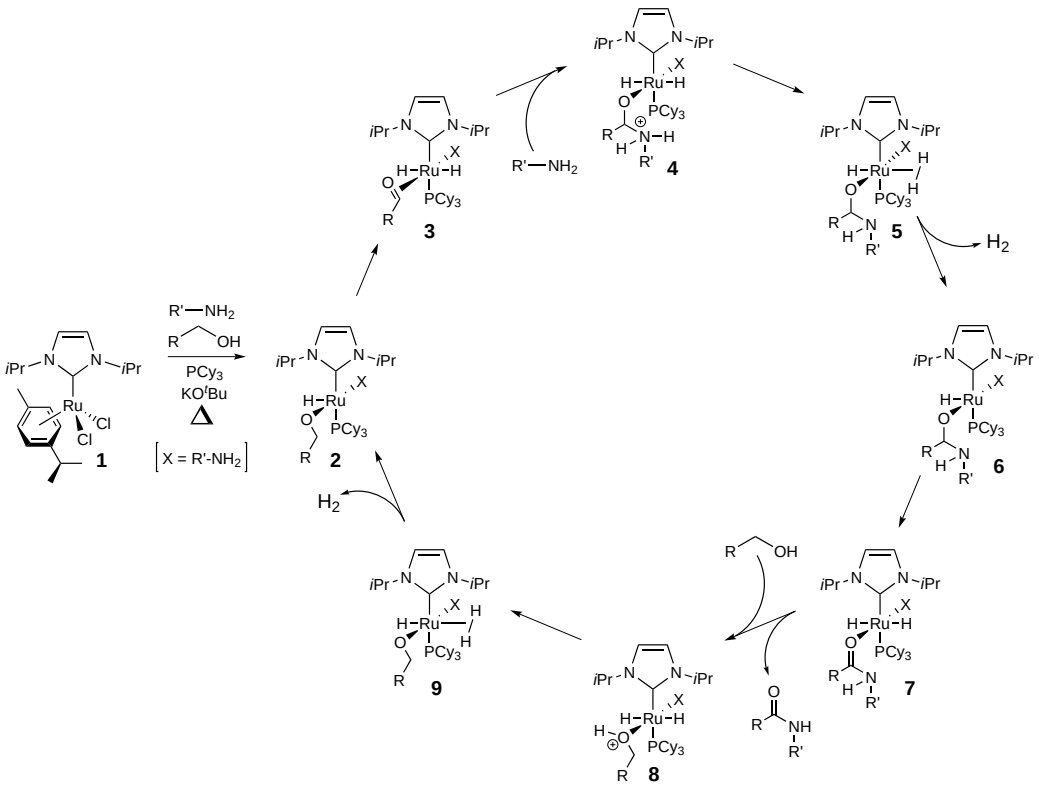


Figure 2.6: The proposed catalytic cycle for the formation of amides by dehydrogenative coupling of primary alcohols and amines with $RuCl_2(I^iPr)(p\text{-cymene})$.

the carbonyl carbon by a molecule of amine to form the hemiaminal complex **4**. Deprotonation of the hemiaminal by the hydride ligand on ruthenium produces the complex **5**, which then loses one molecule of hydrogen gas and forms the 16 e^- complex **6**. This leaves room for a hydride transfer from the hemiaminal to the metal center, creating the 18 e^- complex **7** where the amide is still coordinated to ruthenium. The amide is displaced by attack of a new molecule of alcohol to form complex **8**, and the alcohol is then deprotonated by the hydride ligand on ruthenium forming complex **9** which upon loss of H_2 reforms complex **2** so the catalytic cycle can start all over again.

2.1.4 Traditional methods for the formation of esters

Esters and lactones constitute an important class of compounds in many areas of organic chemistry: Small esters and lactones are produced industrially on a million tonne scale annually for use as solvents and monomers. Esters of fatty acids are used in the food industry as well as for soaps and detergents and a large variety of esters are used as fragrances and flavorings in both food and perfume productions. Polyesters are an important polymer class in the textile and plastic industries and furthermore the ester functionality is present in many important drugs in the pharmaceutical industry, both natural products and synthetic compounds.[44]

The classic method for preparing an ester, known as the Fischer esterification, consists of reacting a carboxylic acid with an alcohol in the presence of an acid catalyst as well as a dehydrating agent at elevated temperatures.[45] Sulfuric acid is often employed as it meets both requirements. Alternatively a carboxylic acid and an alcohol can be reacted in the presence of stoichiometric amounts of DCC as coupling reagent, which activates the carboxylic acid by transforming the hydroxy group into a better leaving group. Catalytic amounts of an acyl-transfer reagent like DMAP is required. This is known as a Steglich esterification.[46] Another way of achieving the same effect would be to transform the carboxylic acid into one of its more reactive derivatives like the acid chloride or the acid anhydride prior to reaction with the alcohol. Both the Fischer esterification and the transformation of an acid into an acid chloride or anhydride require subjecting the carboxylic acid to rather harsh conditions. The Steglich methodology suffers from the drawback of using stoichiometric amounts of DCC, which is a potent allergen and therefore preferably avoided, and thus producing stoichiometric amounts of dicyclohexylurea as byproduct. The reactions are shown in figure 2.7.

Other popular methods for the preparation of esters include the Mitsonobu

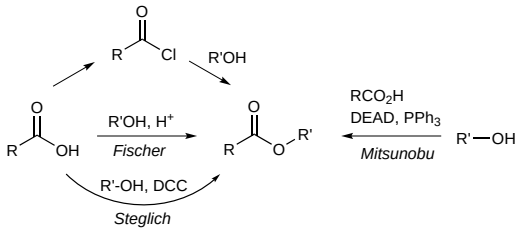


Figure 2.7: Some of the most common ways of preparing an ester: Transformation of a carboxylic acid to a more reactive derivative; the Fischer and Steglich esterifications and the Mitsunobu reaction.

reaction, the Tishchenko reaction, the Favorskii rearrangement and the Baeyer-Villiger oxidation. In the Mitsonobu reaction primary or secondary alcohols and carboxylic acids are transformed into esters by reacting them with equimolar amounts of DEAD and triphenylphosphine (or another azodicarboxylate and phosphine combination), under formation of hydrazinedicarboxylate and phosphine oxide.[47] The reaction runs under fairly mild conditions, with the obvious drawback being the use and formation of stoichiometric amounts of reagents and byproducts, respectively.

The Tishchenko reaction (figure 2.8) is a disproportionation reaction, meaning that the same reagent is both reduced and oxidized in order to form the product. The Tishchenko reaction employs catalytic amounts of either a magnesium or aluminium alkoxide to form esters from aldehydes.[48] Both esters from two molecules of the same aldehyde as well as from two different aldehydes can be formed, but good selectivity is difficult to obtain in the mixed Tishchenko reaction. The reaction conditions are mild, and the reaction is catalytic with respect to the employed metal complex, but it suffers from the serious drawbacks that the substrate scope is limited to aldehydes with no α-protons, and that many side reactions can take place depending on the nature of the catalyst. Among the most commonly observed are the Cannizzaro reaction[49] and the Meerwein-Ponndorf-Verley reduction[50]/Oppenauer oxidation[51], shown in figure 2.8.

The Favorskii rearrangement (figure 2.9) transforms an α-halo ketone to an ester in the presence of an alkoxide base.[52] As is the case for many rearrangements the substrate scope is quite narrow. The Baeyer-Villiger oxidation (or rearrangement) inserts an oxygen atom in the α-position of a ketone by reacting it with a peroxyacid, thereby transforming it to an ester.[53] The migratory aptitude increases with the increasing ability to stabilize a positive charge, favoring

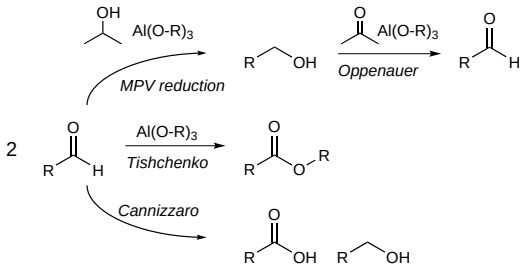


Figure 2.8: The Tishchenko reaction, along with the most common side reactions: The Cannizzaro disproportionation, forming a carboxylic acid and an alcohol, the Meerwein-Ponndorf-Verley (MPV) reduction reducing carbonyl compounds to alcohols and the Oppenauer oxidation, the reverse of the MPV reduction.

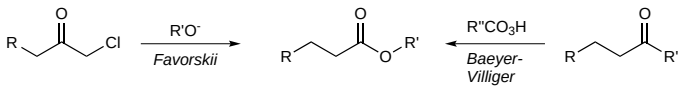


Figure 2.9: The Favorskii rearrangement and the Baeyer-Villiger oxidation or rearrangement.

the formation of esters of tertiary or secondary alcohols over their primary counterparts.[54] This makes the regiochemical outcome predictable, but renders the method unsuitable for the formation of esters of less highly substituted alcohols. Furthermore peroxyacids are very strong acids and thus the method is incompatible with any acid-labile groups present in the molecule. The methods are shown in figure 2.9.

2.1.5 Dehydrogenative ester formation

In recent years more and more methods have been developed that focus on atom-economy and green chemistry. A dehydrogenative route to form esters from alcohols is attractive because the only byproduct is hydrogen gas, which is easy to remove and may even be utilized in further transformations if the reaction were to be run industrially on a large scale. Some methods claim to be dehydrogenative, but are dependent on the presence of a hydrogen scavenger in order to drive the reaction to completion, and thus is more correctly described as being a hydrogen transfer reaction. These methods are obviously less attractive from a 'green chemistry' point of view as they incorporate stoichiometric amounts of a contaminant molecule, thereby making it less clean.

Shvo and coworkers were pioneers in the field of ruthenium catalyzed dehydrogenations. In two papers from 1981 and 1984, respectively, they describe how $Ru_3(CO)_{12}$ catalyzes the formation of esters from aldehydes and alcohols in the presence of diphenyl acetylene as a hydrogen acceptor, and under the same conditions also observed the formation of symmetric esters directly from primary alcohols and of ketones from secondary alcohols.[55] A search for the active catalytic species in the reactions led to the subsequent discovery of the complexes (η^4-tetracyclone)$(CO)_3$Ru and [(η^4-tetracyclone)$(CO)_2$Ru]$_2$, which are believed to be catalytic precursors and was shown to be able to facilitate the dehydrogenation of primary alcohols to esters and secondary alcohols to ketones without the presence of a hydrogen acceptor. This also showed that in the initially reported reaction diphenyl acetylene acted not only as a hydrogen acceptor but also plays a role in the activation of the catalyst.[56] The monomeric complex (η^4-tetracyclone)$(CO)_3$Ru is shown in figure 2.10.

Simultaneously Murahashi and coworkers had developed a similar system,

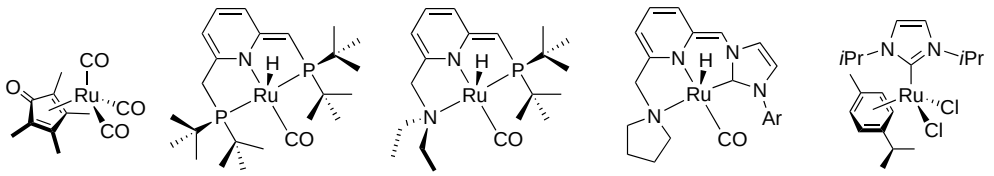


Figure 2.10: Some of the different ruthenium based catalysts used for the dehydrogenative coupling of primary alcohols to form esters. From left to right: The (η^4-tetracyclone)$(CO)_3$Ru complex used by Shvo. The PNP and PNN ruthenium pincer complexes used by Milstein. The NHC ruthenium pincer complex used by Iglesias and Sánchez. The NHC ruthenium complex used by the Madsen group.

namely the complex $RuH_2(PPh_3)_4$, which catalyzes the dehydrogenative condensation of alcohols and diols to form esters and lactones.[57] In the absence of a hydrogen acceptor the yields were good, but they were enhanced in the presence of an appropriate hydrogen acceptor, although at the expense of a lower selectivity for formation of the ester above the corresponding ether and acetal. In particular the reactions of less reactive alcohols benefited greatly from the addition of a hydrogen acceptor. The same catalytic system could also be used for the reaction of aldehydes with alcohols to form esters, but the mixed reaction between R^1CHO and R^2CH_2OH proceeds unselectively and forms a mixture of the four possible products, most likely due to an intermediary reduction of the aldehyde. Similarly, an aldehyde could be reacted with water to form the corresponding carboxylic acid, but only in the presence of a hydrogen acceptor, otherwise the ester is formed.

In 2004 Milstein and coworkers reported the synthesis of a ruthenium PNP complex which catalyzed the acceptorless dehydrogenation of secondary alcohols to ketones;[58] the catalytic scope of the complex was shortly thereafter expanded to include the self condensation of primary alcohols to form esters.[25] In the paper both the PNP and a similar PNN complex of ruthenium was tested; both showed good reactivity, although the PNN complex with the hemilabile amine arm is far superior. Both catalysts could be added to the reaction mixture in only 0.1 mol %, in the presence of 0.1 mol % of KOH in refluxing toluene and gave the esters from the condensation of a variation of primary alcohols in very good to excellent yields. The deprotonated forms of the PNP and PNN ruthenium pincer complexes are shown in figure 2.10.

In 2008 Williams and coworkers reported the use of $Ru(PPh_3)_3(CO)H_2$ in combination with the xantphos ligand as catalyst for the formation of methyl esters from primary alcohols and methanol, using crotononitrile as hydrogen acceptor.[59] The conversion of aldehydes to methyl esters with methanol was also achieved using the same setup. In both cases the yields were very good.

In 2011 Iglesias and Sánchez reported the synthesis of seven variations of

ruthenium pincer hydride complexes, structurally very similar to the ones used by Milstein and coworkers, but with a NHC group instead of the phosphine.[60] The complexes were tested as catalysts for the dehydrogenative formation of esters from primary alcohols as well as the transfer hydrogenation of carbonyl compounds in general. The activities of the complexes were high and the reported yields were excellent. The deprotonated form of the most efficient NHC ruthenium pincer complex is shown in figure 2.10.

A catalytic system based on the same $RuCl_2(I^iPr)(p\text{-cymene})$ complex as the previously mentioned systems for amidation- and imination reactions were published by Madsen and Sølvhøj in 2011.[40] The development and optimization of this particular synthetic method, as well as some mechanistic investigations is described in detail in the following sections. The ruthenium complex used in the Madsen group is shown in figure 2.10.

Other transition metals have also successfully been applied to facilitate these transformations, like iridium, rhodium and rhenium. Suzuki and Katoh presented an amino alcohol-based Ir bifunctional catalyst (figure 2.11) which performed oxidative dimerization of primary alcohols in high yields in the presence of 2-butanone as hydrogen acceptor.[61] Obora and Ishii published the use of a combination of the iridium dimer complex $[CpIrCl_2]_2$ and 2-(methylamino)-ethanol as a catalyst for the methyl-esterification of primary alcohols and diols with methanol using acetone as hydrogen acceptor.[62] An acceptorless system for the dehydrogenation of alcohols based on an iridium PCP pincer complex was published by Gelman and coworkers (figure 2.11); the catalyst was employed for the formation of ketones from secondary alcohols, lactones from diols and esters from primary alcohols.[63]

Grützmacher and coworkers presented the rhodium complex $[Rh(trop_2N)(PPh_3)]$ (figure 2.11) capable of facilitating dehydrogenative coupling of primary alcohols and diols with methanol, water or amines forming methyl esters, acids or amides respectively. The reactions give good yields, but in the presence of cyclohexanol or methylmethacrylate as hydrogen acceptor.[33] One of the most

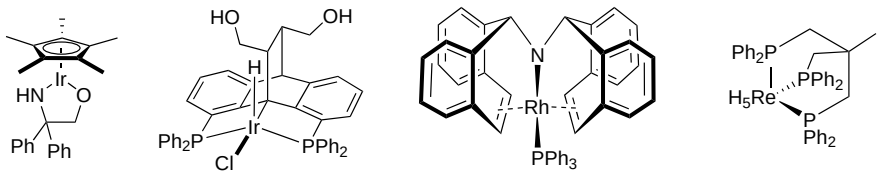


Figure 2.11: Some of the complexes of other transition metals like iridium, rhodium and rhenium employed for the dehydrogenation of alcohols. From left to right: The amino alcohol-based iridium complex by Suzuki and Katoh. The iridium PCP pincer complex by the Gelman group. The rhodium complex from the Grützmacher group. The triphos rhenium complex from the Klankermayer group.

recent additions is the use of a triphos rhenium complex as a homogenous catalyst for the acceptorless dehydrogenation of alcohols presented by Klankermayer and coworkers in 2013 (figure 2.11). The complex catalyzes both the formation of amides from the reaction between primary alcohols and amines and the formation of esters from the self condensation of primary alcohols. The catalyst is very efficient, requiring only a loading of 0.2 mol % and no additives in the case of the amidation reaction and only DABCO for the esterification reaction.[35]

2.2 Development of a new method for dehydrogenative ester formation

The dehydrogenative formation of esters by the homocoupling of primary alcohols described in this thesis was initially observed as a side reaction during the $RuCl_2(I^iPr)(p\text{-cymene})$ catalyzed formation of amides: In the absence of a better nucleophile the employed alcohol reacts with itself and forms a symmetric ester. It was decided to investigate this reaction further, and hereby a side reaction was transformed into a very useful reaction. The general reaction is shown in figure 2.12. The process of developing the method by optimization of the reaction conditions and expansion of the substrate scope is described in the present section.

As was described in the previous section the method presented herein for a dehydrogenative formation of esters is by no means the only of its kind, but it does hold some advantages compared to its predecessors and successors, which makes it an important contribution to the scientific area of dehydrogenative methodologies: The utilized pre-catalyst is easily synthesized from commercially available compounds, it is stable, relatively cheap and not too air sensitive, meaning that reactions can be run using only schlenk techniques and not requiring more expensive equipment like a glovebox. Furthermore, the reaction needs no hydrogen scavengers in order to run and only a few additives are present (catalytic amounts of base and phosphine ligand), which is a great benefit from an atom economical point of view.

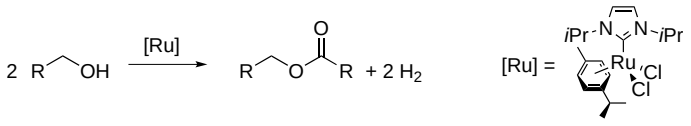


Figure 2.12: The dehydrogenative formation of esters by the homocoupling of primary alcohols catalyzed by the ruthenium complex $RuCl_2(I^iPr)(p\text{-cymene})$.

2.2.1 Optimization of the reaction conditions

The condensation of two molecules of pentanol forming pentyl pentanoate was chosen as the model system. The initial experiment was carried out using 2.5 mol % of $RuCl_2(I^iPr)$(*p*-cymene)and 7.5 mol % of KO^tBu in refluxing dry toluene under an argon atmosphere. The yield was measured by GC/MS to be 34 %, using tridecane as an internal standard. The reaction was tested with and without a phosphine ligand present, and different bases were explored before it became apparent that the yields were not consistent and the initial experiment was not reproducible. One possible explanation for this might be that the reaction is simply too slow at this temperature, causing the catalyst to decompose before the reaction has gone to completion. The solvent was changed to mesitylene, raising the reflux temperature to 165 °C, which made the yields of identical experiments consistent, although it only reached 19 % with the initial conditions.

Base loading Starting with the above mentioned experimental setup a series of experiments were conducted to determine the influence of the base loading on the reaction yield. In refluxing mesitylene in the presence of 2.5 mol % of $RuCl_2(I^iPr)$(*p*-cymene) the loading of KO^tBu was varied from 0 to 28 %. The results are shown in table 2.1 and graphically in figure 2.13. As can be seen from the graph there seems to be a connection between the yield and the amount of base present: The yield increases with increasing amounts of potassium tert-butoxide and peak by addition of approximately 20 mol %, giving a yield of 58 %.

Adding 2.5 mol % of tricyclohexylphosphine to the reaction mixture improved the yield significantly and also diminished the need for the large excess of base. One possible explanation for these findings might be that in the absence of a phosphine ligand to coordinate to the ruthenium the *tert*-butoxide anion plays a double role, acting both as a ligand on ruthenium and as a base. In the presence of a superior ligand, in this case the phosphine, the *tert*-butoxide anion acts only as a base and thus a lower loading is sufficient.

As can be seen from table 2.1 the best conditions proved to be with 10 mol % of potassium *tert*-butoxide and 2.5 mol % of phosphine (entries 9, 10 and 13); this gave a yield of 65–70 %. Omitting the base completely and having only the phosphine present gave virtually no conversion of the starting material (entry 1).

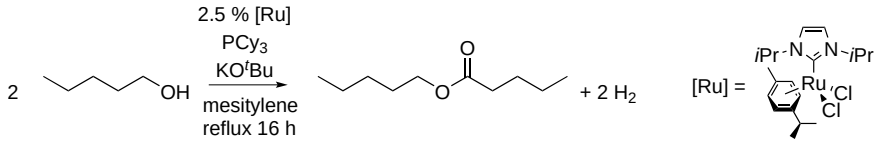


Table 2.1: Reaction yields as a function of base loading.

Entry	KO^tBu loading	PCy_3 loading	Yield	Entry	KO^tBu loading	PCy_3 loading	Yield
1	0 %	2.5 %	1 %	13	11 %	2.5 %	65 %
2	4 %	—	4 %	14	12 %	—	37 %
3	4 %	2.5 %	8 %	15	13 %	2.5 %	56 %
4	6 %	—	17 %	16	14 %	—	42 %
5	7 %	—	11 %	17	16 %	—	51 %
6	7 %	2.5 %	52 %	18	17 %	2.5 %	53 %
7	8 %	—	23 %	19	18 %	2.5 %	45 %
8	8 %	—	19 %	20	19 %	2.5 %	32 %
9	10 %	2.5 %	65 %	21	21 %	—	58 %
10	10 %	2.5 %	70 %	22	21 %	2.5 %	54 %
11	11 %	—	26 %	23	25 %	—	56 %
12	11 %	—	40 %	24	28 %	—	51 %

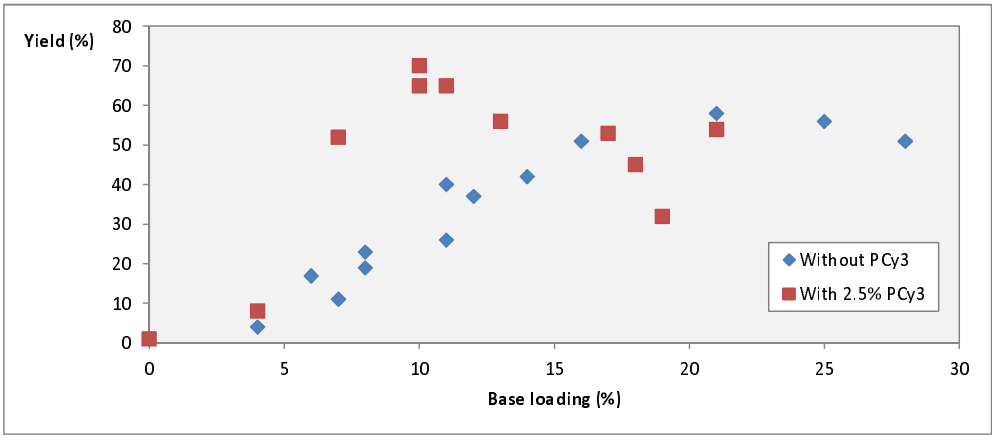


Figure 2.13: The reaction yield as a function of base loading, with and without PPh_3 present.

The nature of the base, ligand and catalyst Subsequently different bases were tested (entries 1–8, table 2.2). As previously observed the reaction did not run at all in the absence of a base. The use of different carbonate bases like K_2CO_3 and $NaHCO_3$ gave yields comparable to when KO^tBu was used (entries 2–5) and the use of Et_3N reduced the yield to a mere 7 % (entry 6), discouraging the further exploration of amine bases. The addition of a hydroxide base, NaOH or KOH (entries 7-8), improved the yield greatly: A maximum yield of 92 % was obtained when employing KOH as the base. The reason for the superiority of the hydroxide bases is unclear; in comparison with the weak carbonate bases there is obviously the sheer difference in basicity to consider, but this does not explain the inferiority of KO^tBu or Et_3N.

A small selection of different phosphine ligands were explored (entries 8–11, table 2.2) but both an increase (P^tBu_3, entry 11) and decrease (PPh_3, entry 10) in cone angle compared to the initially employed tricyclohexyl phosphine resulted in drastically diminished yields. As expected the related tricyclopentyl phosphine gave a comparable yield (entry 9). The addition of the amine ligand DABCO reduced the yield to a mere 11 % (entry 12). Varying the amount of phosphine from between 2.5 mol % to 9 mol % (not shown in the table) showed that the highest yields were obtained by using a slight excess of phosphine as compared to the amount of ruthenium complex, around 4.5 mol %. This gave close to quantitative yield (entry 13, table 2.2). Phosphines, and particularly tricycloalkyl phosphines, are known to form oxides easily, and the contamination of PCy_3 with relatively large amounts of phosphine oxide would be a plausible explanation for the necessity of excess amounts of phosphine for the reaction to run optimally. A subsequent analysis by ^{31}P-NMR of the employed PCy_3 shows clearly the presence of PCy_3O in a ratio of about 1:3 to the unoxidized species, accounting for at least part of the excess.

A study performed by Makarov in the Madsen group showed that all the examined samples of PCy_3 from commercial suppliers contained impurities such as phosphine oxides and phosphites and while PCy_3 could be recrystallized to obtain the pure compound, it was very quickly oxidized again.[64] In the subsequent improvement of the esterification reaction performed by Makarov,[65] which is described in section 2.2.3, the loading of the phosphine was adjusted to one equivalent with respect to the ruthenium compound by employing the tetrafluoroborate salt $PCy_3{\cdot}HBF_4$ instead, as had been proposed by Netherton and Fu.[66]

Attempts were made to lower the reaction temperature by changing the solvent to either xylene or toluene. Toluene gave significantly lower yields. The yields using xylene as solvent were in some cases comparable, but proved to be more inconsistent than when using mesitylene.

The methylimidazolium ruthenium *p*-cymene complex was also tested as

pre-catalyst, but gave no improvement of the yield (entry 14, table 2.2). As control experiments the reaction was also performed using the ruthenium dichloro *p*-cymene dimer as precatalyst, which gave a yield of only 16 % (entry 15, table 2.2). This clearly shows that the N-heterocyclic carbene ligand plays an important role in the reaction. Finally, in the absence of any ruthenium the reaction gave no conversion at all (entry 16, table 2.2).

The reaction conditions from entry 13, giving nearly quantitative yield by GC analysis, were employed as general reaction conditions in the subsequent work with expanding the substrate scope.

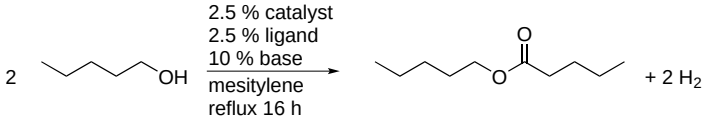


Table 2.2: The yield of the reaction employing different bases, ligands and catalysts.

Entry	Catalyst	Base	Ligand	GC Yield
1	$RuCl_2(I^iPr)$(*p*-cymene)	—	PCy_3	1 %
2	$RuCl_2(I^iPr)$(*p*-cymene)	KO^tBu	PCy_3	70 %
3	$RuCl_2(I^iPr)$(*p*-cymene)	K_2CO_3	PCy_3	71 %
4	$RuCl_2(I^iPr)$(*p*-cymene)	Na_2CO_3	PCy_3	56 %
5	$RuCl_2(I^iPr)$(*p*-cymene)	$NaHCO_3$	PCy_3	68 %
6	$RuCl_2(I^iPr)$(*p*-cymene)	Et_3N	PCy_3	7 %
7	$RuCl_2(I^iPr)$(*p*-cymene)	NaOH	PCy_3	81 %
8	$RuCl_2(I^iPr)$(*p*-cymene)	KOH	PCy_3	92 %
9	$RuCl_2(I^iPr)$(*p*-cymene)	KOH	$PCyp_3$	90 %
10	$RuCl_2(I^iPr)$(*p*-cymene)	KOH	PPh_3	66 %
11	$RuCl_2(I^iPr)$(*p*-cymene)	KOH	P^tBu_3	48 %
12	$RuCl_2(I^iPr)$(*p*-cymene)	KOH	DABCO	11 %
13	$RuCl_2(I^iPr)$(*p*-cymene)	KOH	PCy_3 (4.5 %)	97 %
14	(IMe)Ru(*p*-cymene)Cl_2	KOH	PCy_3 (4.5 %)	90 %
15	[Ru(*p*-cymene)Cl_2]$_2$	KOH	PCy_3 (4.5 %)	16 %
16	—	KOH	PCy_3	0 %

2.2.2 Expansion of the substrate scope

The best set of reaction conditions from the optimization experiments described in the previous sections gave 97 % yield by GC analysis (entry 13, table 2.2). The reaction is shown in figure 2.14. This reaction was repeated on a 10 mmol scale and worked up, obtaining an isolated yield of 70 % (entry 1, table 2.3). The reaction was performed in mesitylene as solvent, which has a boiling point

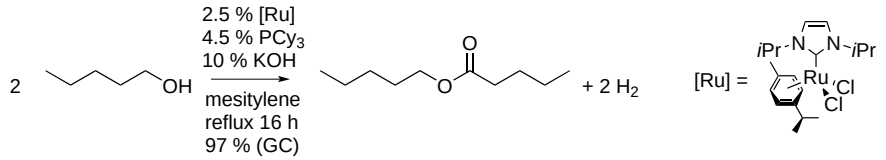


Figure 2.14: The optimized reaction conditions for the dehydrogenative formation of pentyl pentanoate from pentanol.

of 165 °C. While the high reflux temperature was necessary in order to make the reaction run properly, it led to some obstacles in the work-up procedure. Evaporating mesitylene on a rotary evaporator required elevated temperatures, but this caused the product to be conveyed with the solvent to the collecting flask, even though pentyl pentanoate has a boiling point of 207 °C. This problem was overcome by pouring the reaction mixture directly onto a dry column and eluting from heptane to ethyl acetate with 2 % increments, following the procedure for dry column vacuum chromatography published by Pedersen and Rosenbohm in 2001.[67] Thereby the mesitylene was contained in the first couple of fractions, while the ester was obtained a pure colorless oil in two of the later fractions. This work-up procedure was applied to all reactions described in the current section, with the only variation being the gradient.

The scope of the reaction was expanded to include the longer primary aliphatic alcohols decanol and undecanol (entry 2 and 3, table 2.3) in good yields. Smaller alcohols were more difficult as both they and their resulting esters have very low boiling points compared to the solvent. Thus no reliable yields can be reported for the self condensation reactions of ethanol and propanol. When the alcohol becomes branched, like 2-ethylhexanol (entry 4) and 2-methylpentanol (entry 5) the reaction still works, but the yield drops significantly. The reason for this is believed to be due to the fact that decarbonylation is an observed side reaction, which may be increasingly significant with increasing branching on C2.

Lactonisation of diols under the same conditions proceed very well for the formation of γ– and δ–lactones (entry 6–8, table 2.3). Formation of γ–butyrolactone was also tested as a neat reaction in which case it gives 60 % isolated yield with 1.25 mol % ruthenium complex (not shown in table). Lactonisation of 1,3-propandiol and 1,6-hexandiol, to form β–propiolactone and ε–caprolactone, respectively, was attempted but was unsuccessful. In the case of 1,3-propandiol no β-propiolactone was observed by GC/MS at all. In the case of 1,6-hexandiol traces of ε–caprolactone was observed by GC/MS, but it was not present in a sufficient yield to be isolated. From the chromatogram it was apparent that most of the starting material was left unreacted.

Benzylic alcohols in general gave very low yields (entries 10–13, table 2.3).

Surprisingly, this proved to be mainly due to decarbonylation as a significant side reaction, which is believed to be caused by the high temperature. Benzyl alcohol (entry 10) itself gives 31 % ester, but the extent of decarbonylation is not known as benzene was not detected by the employed GC method. *p*-Methylbenzyl alcohol gives 24 % ester and 63 % toluene (entry 11) and *p*-methoxybenzyl alcohol gives 19 % ester and 48 % anisole (entry 12). *p*-Chlorobenzyl alcohol (entry 13) gives rise to several compounds: 45 % of the ester along with 15 % of chlorobenzene is formed, but traces of the two different mono-chlorinated benzyl benzoates are also observed, showing that dehalogenation also takes place to some extent.

For all of the benzylic alcohols goes that the reaction has not run to completion after 17 hours, as unreacted alcohol is still present in the chromatogram. In the case of *p*-methylbenzyl alcohol and *p*-chlorobenzyl alcohol formation of the corresponding aldehyde is observed. Since *p*-methoxybenzyl alcohol was later discovered to be contaminated with the aldehyde prior to reaction it is not possible to tell whether more is formed during the reaction of this particular substrate. None of the aldehyde is observed with benzyl alcohol as substrate.

Although decarbonylation is mainly observed with benzylic alcohols or aliphatic alcohols that are branched in the β-position, it does still take place to some extent with a substrates like 2-phenylethanol, where the aromatic ring is moved one carbon away from the hydroxy group. In this case formation of 7 % of toluene is observed (entry 9).

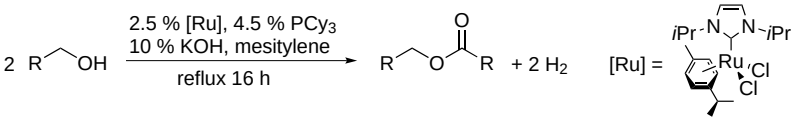
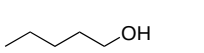
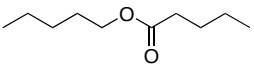
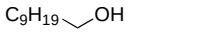
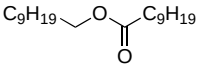
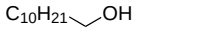
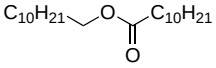
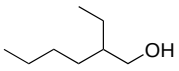
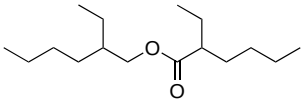
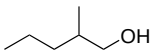
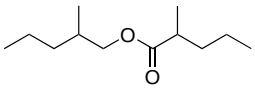
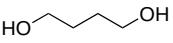
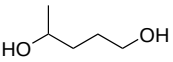
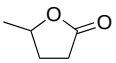
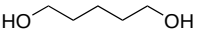
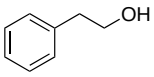
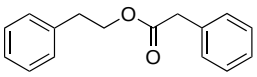
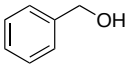
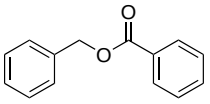
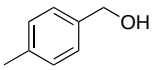
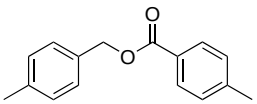
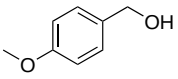
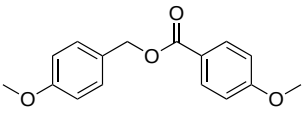
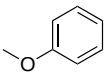
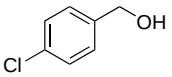
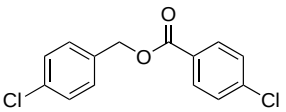
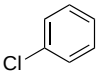
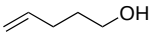
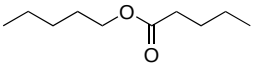


Table 2.3: Expanding the scope of the reaction to include a variety of substrates.

Entry	Substrate	Products	Yield (%)	GC Yield (%)
1			70	97
2			81	86
3			76	84
4			64	63

continues...

Entry	Substrate	Products	Yield (%)	GC Yield (%)
5			45	49
6			71	86
7			78	82
8			61	63
9			48	52
			—	7
10			31	27
11			24	—
			—	63
12			19	—
			—	48
13			45	—
			—	15
14			24[a]	13

[a]Inseparable mixture of the saturated and unsaturated ester

The dehydrogenative nature of the reaction limits the substrates to saturated alcohols as unsaturations are partly reduced by the developed hydrogen. This was observed when attempting to couple two molecules of pent-4-en-1-ol, which resulted in an inseparable mixture of the fully saturated and partly unsaturated ester (entry 14, table 2.3).

The isolated yields in general are somewhat lower than the GC yields. This may of course be due to an uncertainty in the calibration curve, as inaccuracies in measuring out the internal standard and the alcohol may result in some variation in the detected yield. But other causes may be that even tiny mechanical losses in experiments on such a small scale results in a large percent wise decrease in yield and, perhaps most crucially, that many of the products are volatile compounds which are conveyed with the solvent when evaporating the latter during the purification process.

Attempts were made to perform condensations between two different primary alcohols, but these resulted in a mixture of products. The reaction between ethanol and pentanol resulted in a statistical mixture of pentyl acetate, pentyl pentanoate and ethyl pentanoate. Ethyl acetate was not observed by GC/MS but is most likely present in comparable amounts. Transesterifications with primary alcohols were shown to take place readily under the employed reaction conditions and therefore the observed scrambling may also take place after the initial ester formation as a consequence of transesterification. The reaction between pentanol and benzyl alcohol also resulted in a statistical mixture of the four different possible esters.

Reactions between a primary and a secondary or tertiary alcohol were also attempted. The reaction between pentanol and either 2-propanol, phenol or *t*-butyl alcohol resulted only in the formation of pentyl pentanoate from the self-condensation of pentanol. No transesterifications were observed with neither secondary nor tertiary alcohols nor phenol.

The reaction between pentanol and 1-phenylethanol gave a mixture of products: The major product was pentyl pentanoate, but methyl phenyl ketone

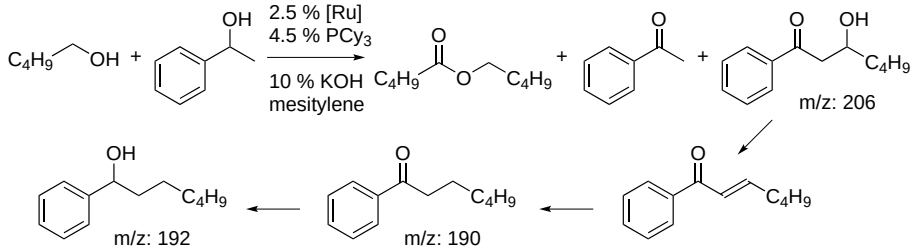


Figure 2.15: The reaction between pentanol and 1-phenylethanol gave rise to a mixture products.

from the dehydrogenation of 1-phenylethanol was also present. The presence of an enolizable ketone further resulted in the formation of both 3-hydroxy-1-phenylheptan-1-one, 1-phenylheptan-1-one and 1-phenylheptan-1-ol from the aldol reaction between pentanal and methyl phenyl ketone and the subsequent hydrogenation of the products. The reaction is shown in figure 2.15.

2.2.3 Subsequent improvements

A subsequent study on the method performed by Makarov in the Madsen group was published in 2013.[65] This study showed that the catalyst loading could be reduced to 1.25 % and the reaction temperature lowered to 110 °C without compromising the reaction yield by adding 16.7 mol % of Mg_3N_2 to the reaction mixture. The improvement of the method also made it possible to perform the condensation of benzylic alcohols in acceptable yields, as the decarbonylation of benzylic substrates that impaired the reaction under the original reaction conditions occurred to a much lesser extent under the new reaction conditions, probably due to the lowering of the reaction temperature.

Furthermore, it was discovered that under these new reaction conditions 1-phenylethanol reacted with itself in what can be described as a dehydrogenative Guerbet reaction to give 1,3-diphenylbutan-1-one in 95 % yield. The reaction is shown in figure 2.16. This protocol could be transferred to other secondary alcohols with a slight change of conditions. It was speculated that the relatively high acidity of the α-protons on methyl phenyl ketone made it possible to perform the Guerbet reaction employing only catalytic amounts of KO^{t}Bu and the relatively weak base Mg_3N_2, but when the substrates were aliphatic secondary alcohols the application of equimolar amounts of stronger bases, like KOH, Li_3N, KO^{t}Bu or LDA, was necessary. The best results were obtained with one equivalent of KOH, in which case the use of KO^{t}Bu could be omitted completely. The reaction conditions are given in figure 2.16. A variety of benzylic alcohols and aliphatic secondary alcohols with carbon chains of six or longer could be converted to the corresponding Guerbet products in this way. Attempts to perform the reaction on alkan-3-ols failed.

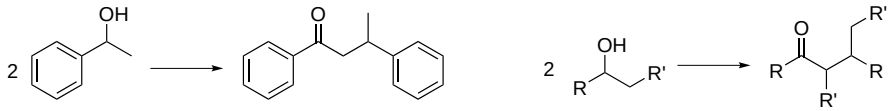


Figure 2.16: On the left: The dehydrogenative Guerbet reaction of 1-phenylethanol: 1.25 % of $RuCl_2(I^iPr)(p\text{-cymene})$, 1.25 % of $PCy_3{\cdot}HBF_4$, 3.75 % of KO^{t}Bu , 16.7 % of Mg_3N_2 in refluxing toluene. 95 %. On the right: The general dehydrogenative Guerbet reaction of secondary alcohols: 2 % of $RuCl_2(I^iPr)(p\text{-cymene})$, 2 % of $PCy_3{\cdot}HBF_4$, 106 % of KOH in refluxing toluene.

2.2.4 Attempts to use other nucleophiles

As has been elaborated in the previous sections $RuCl_2(I^iPr)$(*p*-cymene) can be employed as a catalyst for the dehydrogenative coupling of primary alcohols with N– and O–nucleophiles, thereby forming new C–N and C–O bonds, respectively. A series of experiments were conducted attempting to use carbon nucleophiles in a similar reaction with primary alcohols, thus expanding the scope of the catalyst to include C–C bond formation as well.

The general idea was to use substrates like carbonyl compounds, which would form enolates under the basic reaction conditions employed. A variety of ketones, 1,3-diketones, malonate esters and similar compounds were submitted to the same set of standard reaction conditions: The potential nucleophile was reacted with pentanol in the presence of 5 mol% of $RuCl_2(I^iPr)$(*p*-cymene) and 10 mol% of ^{t}BuOK in refluxing toluene under argon. After 16 hours the experiments were stopped and analyzed by GC/MS. The substrates along with the reaction conditions and the major products are shown schematically in table 2.4.

Ketones and 1,3-diketones The reaction between acetophenone and pentanol (entry 1, table 2.4) resulted in the formation of pentyl pentanoate from the self condensation of pentanol as well as some 1-phenylethanol from the reduction of acetophenone, presumably by the hydrogen developed from the dehydrogenation of pentanol. Addition of styrene to the reaction mixture as a potential hydrogen scavenger did decrease the extent of reduction of the ketone, but did not otherwise cause a change in the product composition. This means that the reduction of acetophenone is not a competing reaction, but rather that pentanol is just a better nucleophile. Employing instead diphenyl acetone (entry 2), which is easier enolized, gave rise to more or less the same result: The primary product was pentyl pentanoate and diphenyl acetone was partly reduced to 1,3-diphenylpropan-2-ol, but in this case trace amounts of the saturated cross condensation product was observed.

Interestingly, when employing 1,3-diketones like acetyl acetone and cyclohexan-1,3-dione (entries 3 and 4) no formation of pentyl pentanoate was observed. The major product from the reaction between acetyl acetone and pentanol was pentyl acetate. For the reaction between cyclohexan-1,3-dione and pentanol the major product was the reduced aldol condensation product from two molecules of the diketone, along with small amounts of both the saturated and unsaturated condensation product between the diketone and pentanol. Cyclohexenone and cyclohexanone were also observed, most likely arising from the reduction of one of the ketones to an alcohol, followed by elimination and reduction of the resulting double bond.

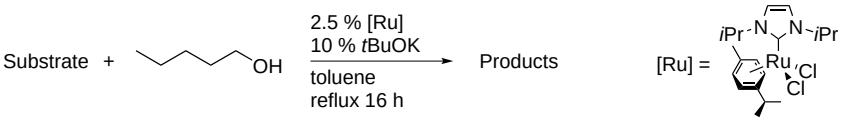
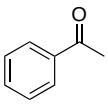
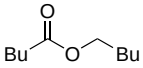
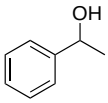
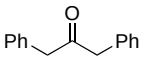
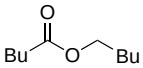
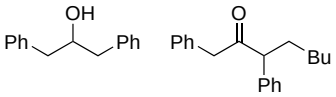
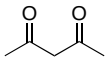
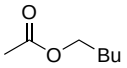
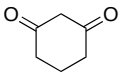
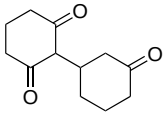
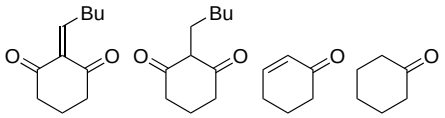
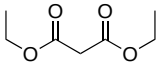
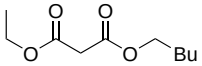
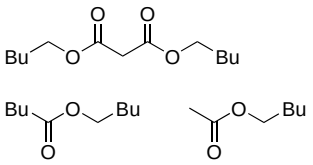
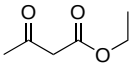
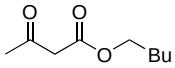
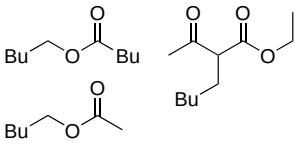
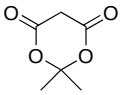
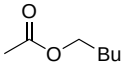
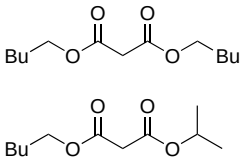
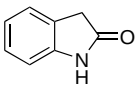
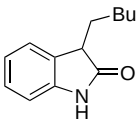
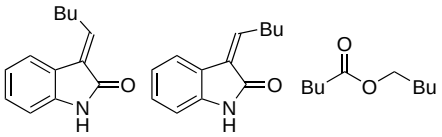
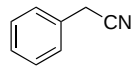
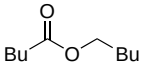
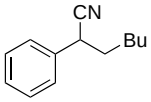
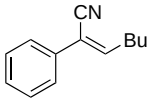


Table 2.4: The reaction between various potential C-nucleophiles and pentanol.

Entry	Substrate	Major product	Byproducts
1			
2			
3			—
4			
5			
6			
7			
8			

continues. . .

Entry	Substrate	Major product	Byproducts
9			 

β-Oxo-esters Reacting diethyl malonate with pentanol (entry 5, table 2.4) under the standard conditions resulted mainly in ethyl pentyl malonate from transesterification of one ester group and to a lesser extent dipentyl malonate from transesterification of both ester groups. Some formation of pentyl pentanoate and small amounts of pentyl acetate and ethyl pentanoate were also observed. When employing the β-keto ester ethyl acetoacetate (entry 6) the same trend was observed. The reaction gave rise mainly to pentyl acetoacetate from the transesterification reaction and some pentyl pentanoate along with equal amounts of the saturated cross condensation product was observed. Traces of pentyl acetate and ethyl pentanoate were also present.

When employing Meldrum's acid (entry 7) the main product was pentyl acetate, along with dipentyl malonate and traces of isopropyl pentyl malonate. While the presence of dipentyl malonate can be explained by a double transesterification of Meldrum's acid with pentanol, the occurence of pentyl acetate and isopropyl pentyl malonate requires a little more speculation. One possibility is that a single transesterification between Meldrum's acid and pentanol occurs, producing acetone and the mono pentyl ester of malonic acid. The latter then decarboxylates under formation of pentyl acetate. The reaction is shown in figure 2.17. The formed acetone would likely be reduced to propan-2-ol which could react with dipentyl malonate, forming the observed isopropyl pentyl malonate.

Other substrates The reaction between 2-indolinone and pentanol (entry 8, table 2.4) initially gave only trace amounts of three different cross condensation products, i.e. 3-pentylindolin-2-one and two different unsaturated analogs, along with traces of pentyl pentanoate. The presence of styrene as a hydrogen scavenger increased the formation of the cross condensation products remarkably, with the major product being 3-pentylindolin-2-one. When the reaction was run in an open system to better facilitate the removal of hydrogen the product composition was changed in favor of the unsaturated condensation product, but the formation of pentyl pentanoate increased, along with several other unidentified byproducts. When the reaction was run in the presence of 1 equivalent of base instead of just 10 mol % the reaction was faster, but favored formation of the saturated condensation product over the unsaturated one.

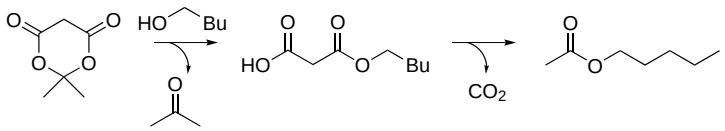


Figure 2.17: One possible explanation for the formation of pentyl acetate from Meldrum's acid and pentanol, forming acetone and carbon dioxide as byproducts.

The reaction between benzyl cyanide and pentanol produced pentyl pentanoate as the major product, but formation of the cross condensation products, saturated as well as unsaturated, was also observed. In addition hereto traces of a variety of different byproducts from the reduction of the cyanide and the reaction of the resultant amine with pentanol was also observed.

Nitromethane and barbituric acid (not in the table) were also employed as possible substrates, but no reaction was observable by GC/MS. Cyclopentadiene (not in the table) was also employed, but resulted only in formation of pentyl pentanoate and different reduced forms of the cyclopentadiene dimer. Cyclooctane was tested in a reaction with no pentanol present in order to test the efficiency of the $RuCl_2(I^iPr)(p\text{-cymene})$ catalyst as hydrogen abstractor from unfunctionalized hydrocarbons, but only traces of cyclooctene was observed.

Conclusive remarks Some conclusions can be drawn from these preliminary experiments which may prove useful should one wish to further explore the possibilities of employing carbon nucleophiles in the $RuCl_2(I^iPr)(p\text{-cymene})$ catalyzed reaction with primary alcohols

Firstly, it seems clear that the carbon nucleophile has to be of a considerate strength to compete with the ester formation between two molecules of alcohol. No ester groups can be present in the substrate because transesterification occurs readily under the reaction conditions and functionalities which are easily reduced, i.e. C=C double bonds, regular ketones and cyanogroups, should be avoided. The carbonyl group should not be too electrophilic, as both the self-condensation of the carbon nucleophile and attack of the alcohol nucleophile on the carbonyl carbon are competing reactions.

The most promising candidate from these experiments is the 2-indolinone and therefore amides with an acidic α-proton would seem to be the obvious starting point for a subsequent investigation.

2.3 Reaction mechanism

It was assumed that the $RuCl_2(I^iPr)(p\text{-cymene})$ catalyzed dehydrogenative coupling of primary alcohols to form esters would follow the same general mechanism as the coupling of amines and alcohols to form amides catalyzed by the same complex. Several experiments were set up in order to test this hypothesis and their outcome as well as the catalytic cycle based on the findings are described in the current section.

2.3.1 Preliminary mechanistic investigations

Hydrogen development The reaction was believed to be dehydrogenative with the release of two equivalents of molecular hydrogen per ester molecule formed. In order to prove this point the gas developed during the reaction was collected and measured volumetrically. A standard experiment, converting 1 mmol of pentanol to pentyl pentanoate, was run and the developed gas collected in a graduated cylinder. The dehydrogenative conversion of 1 mmol of alcohol into 0.5 mmol of ester should give 1 mmol of hydrogen gas. The GC yield of the reaction was measured to be 85 % which should then give 0.85 mmol of hydrogen. According to the law of ideal gasses 0.85 mmol of hydrogen takes up a volume of 20.4 ml. A total volume of 17.5 ml was collected, corresponding to 86 % of the theoretical amount. When taking into account the possibility of a mechanical loss of hydrogen from small leaks in the experimental setup as well as the fact that the gas may not act exactly as an ideal gas, the experiment serve as a strong indicator that the stoichiometry of the reaction is indeed as expected and two equivalents of gas are developed during the course of the reaction.

The gas development was followed over time: The reaction seems to have run to completion already after two hours. The reaction time is confirmed by following the GC yield of the reaction over time. Both experiments are illustrated graphically in figure 2.18.

To demonstrate that the developed gas was indeed hydrogen an experiment, identical to the one described above, was set up. The gas developed in this reaction was transferred to another reaction flask where it was used in the catalytic hydrogenation of diphenyl acetylene to 1,2-diphenylethane, following a procedure by Felpin from 2010.[68] Both 1,2-diphenylethane and stilbene from the reduction of diphenyl acetylene was observed, which would not be possible if the developed gas was not hydrogen. From these experiments it was concluded that the reaction is dehydrogenative and that two equivalents of hydrogen is released for each ester molecule formed.

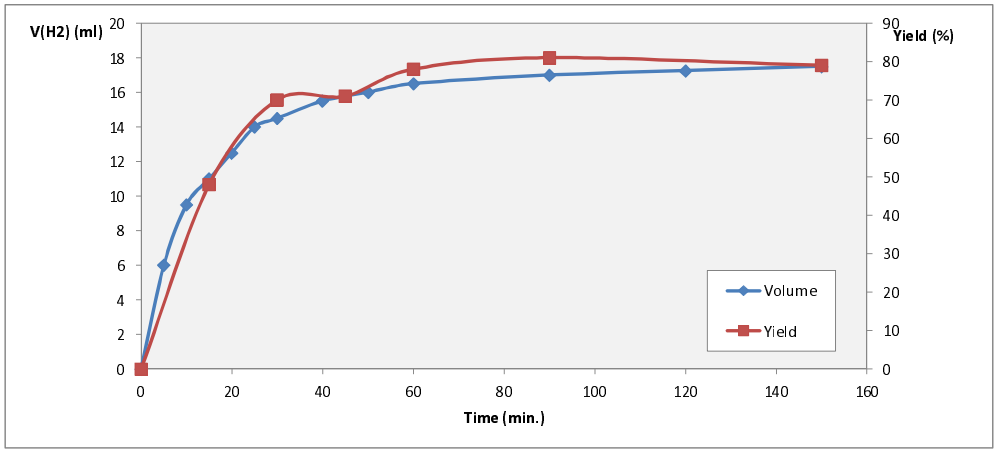


Figure 2.18: Development of hydrogen gas and reaction yield as a function of time.

Reaction intermediates Benzaldehyde was submitted to the reaction conditions in order to test whether an aldehyde disproportionation reaction (Tishchenko reaction) might be a possible mechanism. The reaction showed formation of trace amounts of benzyl benzoate along with the formation of benzyl alcohol. This could be an indication that the aldehyde is being reduced to the alcohol, and the alcohol subsequently transformed into the ester. When the same experiment was repeated in the presence of a small amount of alcohol (pentanol) the yield increased significantly. This supports the hypothesis that the reduction of the aldehyde to the alcohol is a prerequisite for the formation of the ester, because the presence of pentanol provides an initial source of hydrogen, thus resulting in a faster reduction of the aldehyde and therefore a higher yield for the formation of the corresponding ester.

A similar experiment with *p*-methoxybenzaldehyde also showed the formation of trace amounts of *p*-methoxybenzyl alcohol from reduction of the aldehyde and the corresponding ester, along with traces of the decarbonylated product, anisole. The fact that only trace amounts of anisole is present indicates that also the decarbonylation does not happen directly from an aldehyde in solution, but rather from an aldehyde generated on ruthenium, which in turn arises from an alcohol coordinated hereto.

When *p*-methylbenzaldehyde and benzyl alcohol was reacted 1:1 an equally distributed mixture of four different esters was observed, along with the reduced aldehyde. Following the reaction over time shows that the formation of the four esters follow the same rate, but also that relatively large amounts of the reduced aldehyde is formed fast. Already at the first measuring point (T=15 min) the peak for *p*-methoxybenzyl alcohol is comparable to the peak for benzyl alcohol.

This indicates that the hydrogen gas liberated at the beginning of the reaction is used for reduction of the aldehyde, forming an alcohol which then enters the catalytic cycle.

In general no free aldehydes are observed in the reactions where only alcohols are added as substrates, with exception of *p*-chlorobenzyl– and *p*-methoxybenzyl alcohol.

Deuterium scrambling experiments An experiment was conducted where benzyl alcohol-α,α-d_2 was subjected to the standard reaction conditions. The intention was to investigate the possible exchange of hydrogen and deuterium during the reaction. The experiment was performed in deuterated mesitylene to ensure that any hydrogen incorporation would not be a result of an exchange with the solvent, leaving only the hydroxy group on the benzyl alcohol and the base (potassium hydroxide) as potential hydrogen sources. After two and a half hours the reaction was stopped and the unreacted benzyl alcohol isolated. From the proton NMR spectrum one can clearly see a signal from the benzylic protons, meaning that some incorporation of hydrogen has taken place. The benzylic area, shown in figure 2.19, shows a sharp singlet from benzyl alcohol and a broad triplet from mono-deuterated benzylic alcohol. Integration of both peaks together gives an integral of 1 compared to the 5 aromatic protons. This means that 50 % of the deuterium on the original benzyl alcohol-α,α-d_2 has been exchanged for hydrogen, since the integral would be 0 for the fully deuterated species and 2 for the fully hydrogenated species. This integral is close to equally distributed between the singlet and the triplet (exactly 0.42:0.54), which means that 54 % of the dideuterated benzylic alcohol has been transformed to the monodeuterated benzylic alcohol, and 21 % has been transformed to the regular

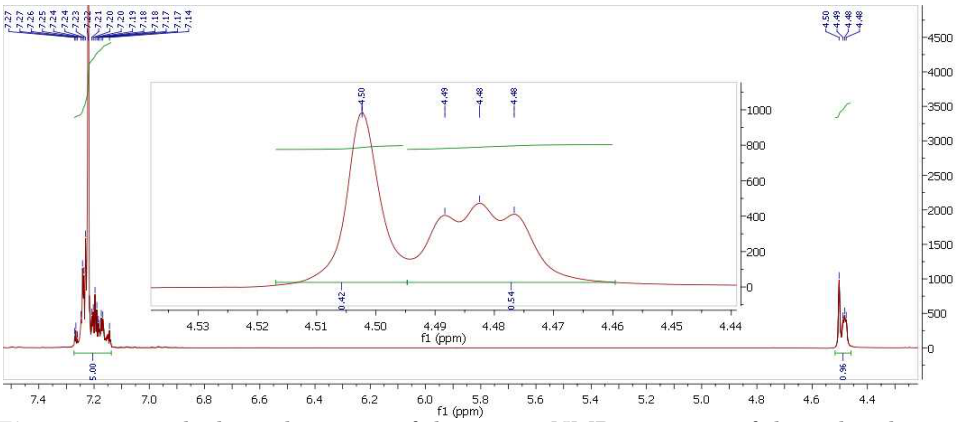


Figure 2.19: The benzylic region of the proton NMR spectrum of the isolated starting material after 2½ hours.

benzylic alcohol. From these numbers follow that the amount of unaltered deuterated alcohol must be 25 %.

An identical reaction was conducted and stopped after 16 hours, whereafter the product and starting material were isolated. Now the isolated starting material contained 62 % hydrogen and 38 % deuterium, distributed between 31 % of the dihydrogenated alcohol, 58 % of the monodeuterated alcohol and 11 % of the dideuterated alcohol. The obtained benzyl benzoate contained 64 % hydrogen and 36 % deuterium in the benzylic position, the same ratio as for the starting material within the margin of statistical error, with a distribution of 37 % of the fully hydrogenated ester, 55 % of the monodeuterated ester and 8 % of the dideuterated ester. The distributions are shown in figure 2.20.

The final distribution between hydrogen and deuterium is 2:1 whereas in the starting material it is 1:2, i.e. one hydrogen from the hydroxy group and two deuterium atoms in the benzylic position. At first this may seem like an inconsistency, but it should be noted that in the final distribution only the protons at the benzylic position are taken into account and not the one on the hydroxy group, as the latter cannot be quantified in a reliable way by NMR due to the rapid hydrogen-deuterium exchange between hydroxy group and solvent. Furthermore, a total of 10 % of KOH compared to the alcohol is present in the reaction mixture, as well as an unknown amount of water from solvents and reagents that may not have been dried completely prior to use, and therefore additional hydrogens are available.

The observed results indicate that the initial β-hydride elimination to form

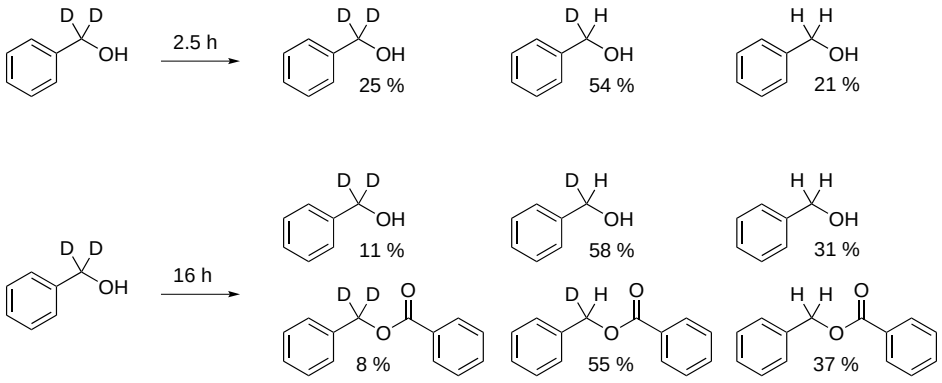


Figure 2.20: Top: The distribution between deuterium and hydrogen in the unreacted starting material after two and a half hours. Bottom: The distribution between deuterium and hydrogen in the product and in the unreacted starting material after 16 hours. Reaction conditions for both reactions are 2.5 % of $RuCl_2(I^iPr)(p\text{-cymene})$, 4.5 % of PCy_3 and 10 % of KOH in refluxing mesitylene-d_{12}

benzaldehyde is a reversible reaction, because otherwise no deuterium exchange in the starting material would occur. More importantly it also implies that the catalytically active species is a ruthenium dihydride and substantiates that the catalytic cycle for the ester formation is similar to the proposed cycle for the amidation reaction.

2.3.2 The proposed catalytic cycle

Based on these preliminary mechanistic investigations, as well as the mechanism deduced for the amidation reaction,[39] the following catalytic cycle for the reaction was proposed, shown in figure 2.21. The very first step is the loss of *p*-cymene from the pre-catalyst **1**. This is confirmed by GC/MS, where the appearance of a peak for *p*-cymene is observed almost immediately. The two chloride ligands are then replaced with hydrides through alkoxide substitution and β-hydride elimination. This type of hydride introduction is a known mechanism for ruthenium(II) chloride complexes, and previously complexes like [(*p*-cymene)Ru-(μ-Cl)$_3$RuCl(H$_2$)(PCy$_3$)] has been isolated and characterized by X-Ray.[43] This results in the ruthenium dihydride complex **2**, which we believe to be the catalytically active species.

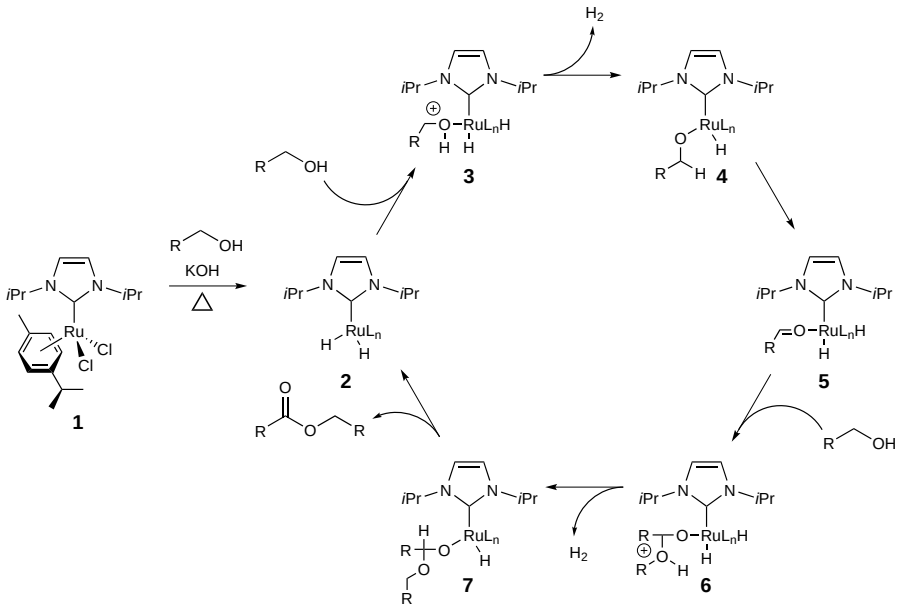


Figure 2.21: The proposed catalytic cycle for the dehydrogenative formation of esters from primary alcohols with a Ru-NHC complex.

From here the catalytic cycle is likely to proceed as follows: One molecule of alcohol coordinates to **2** to give the complex **3**. From **3** hydrogen gas is released by transfer of hydrogen to hydride, furnishing the complex **4**. β-Hydride elimination from **4** yields the aldehyde complex **5**. Nucleophilic attack on the coordinated aldehyde by a second molecule of alcohol yields the hemiacetal complex **6**, from which is released a second molecule of hydrogen gas by transfer of hydrogen to hydride, under formation of the complex **7**. From **7** a β-hydride elimination releases the ester and regenerates the active catalyst **2**.

2.4 Summary and conclusions

To summarize; a new atom economical method for the dehydrogenative formation of esters from primary alcohols has been developed. The reaction is catalyzed by the ruthenium N-heterocyclic carbene complex $RuCl_2(I^iPr)(p$-cymene), which has previously been shown to catalyze other dehydrogenative reactions with primary alcohols. By screening the effect of different additives, solvents and loadings on the self condensation of pentanol, the optimal reaction conditions were found to be 2.5 mol % of $RuCl_2(I^iPr)(p$-cymene), 4.5 mol % of PCy_3 and 10 mol % of KOH in refluxing mesitylene, which gave the ester in nearly quantitative yield determined by GC analysis.

The substrate scope was subsequently expanded to include a range of different straight-chain and branched primary aliphatic alcohols, which reacted to give the corresponding esters in moderate to excellent yields. Condensations of diols also proceeded uneventfully, affording the corresponding lactones in good yields. Benzylic alcohols could also be used as substrates, but the yields were generally poor due to decarbonylation of the substrate as a considerable side reaction.

Some preliminary mechanistic investigations were performed. The developed gas was quantified and identified by a tandem catalytic hydrogenation of diphenyl acetylene, confirming that the reaction is indeed dehydrogenative with the release of two equivalents of hydrogen gas as assumed. The failure to apply aldehydes directly in the reaction rules out a disproportionation mechanism (Tishchenko) and suggests that the intermediary aldehyde stays coordinated to ruthenium until it is released as an ester. From deuterium scrambling experiments it was concluded that a reversible β-hydride elimination takes place, implying that a ruthenium dihydride species is the catalytically active species. A catalytic cycle consistent with these findings as well as with previous knowledge in the field was proposed.

The methodology is neither the first nor the only of its kind, but it does hold some advantages compared to similar methods. The catalyst is easy to

synthesize from commercially available materials, it is stable and does not require the use of a glovebox. The reaction is dehydrogenative by itself, obviating the need for a hydrogen scavenger in the reaction mixture, which is particularly important from a 'green chemistry' point of view. The yields in general are good and the substrate scope is fairly broad, although limited to the formation of symmetric esters from saturated alcohols. Most importantly the study of this reaction has provided valuable insight to the catalytic cycle of the NHC ruthenium complex in question and dehydrogenative ester formation in general.

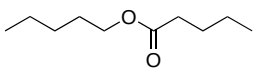
2.5 Experimental part

All solvents used were of HPLC grade, all chemicals were bought from Sigma Aldrich, unless otherwise stated. $RuCl_2(I^iPr)$(*p*-cymene) was synthesized following a published procedure.[27] For dry column vacuum chromatography (DCVC)[67] was used Merck Silica Gel 60, 0.015-0.040 mm. Reactions were monitored by GCMS on a Shimadzu GCMS-QP5000 instrument. NMR spectra were recorded on a Varian Mercury 300 MHz instrument or a Bruker 400 MHz instrument. Chemical shifts were measured relative to the signals of residual $CHCl_3$ (δ_H 7.26 ppm, δ_C 77.16 ppm)[69] and are reported in ppm from lowest to highest field. Mass Spectrometry was performed on a Shimadzu GCMS-QP5000 instrument.

General procedure for $RuCl_2(I^iPr)$(*p*-cymene) catalyzed ester formation

$RuCl_2(I^iPr)$(*p*-cymene) (0.0115 g; 0.025 mmol; 2.5 mol %), PCy_3 (0.0126 g; 0.045 mmol; 4.5 mol %) and KOH (0.0056 g; 0.1 mmol; 10 mol %) was placed in an oven dried schlenk flask. The flask was evacuated and purged with argon three times. The primary alcohol (1 mmol; 0.5 mmol in the case of diols) was mixed with anhydrous mesitylene (1 ml), added to the flask and the reaction mixture refluxed for 16 hours under argon atmosphere. The reaction mixture was cooled down and purified directly by dry column vacuum chromatography.

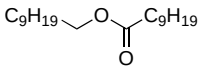
Pentyl pentanoate



Prepared from pentanol. Purified by DCVC, eluting from pentane to ethyl acetate, 2 % increments, to yield the product as a slightly yellow oil in 70 % yield. (GC yield: 97 %). ^{1}H-NMR(300 MHz, $CDCl_3$) δ 3.92 (t, J = 6.7 Hz,

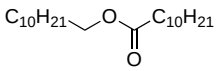
2H), 2.16 (t, J = 7.5 Hz, 2H), 1.62–1.40 (m, 4H), 1.32–1.11 (m, 6H), 0.91–0.70 (m, 6H). ^{13}C-NMR(75 MHz, $CDCl_3$) δ 174.0, 64.4, 34.2, 28.4, 28.2, 27.2, 22.4, 22.4, 14.0, 13.8. MS: m/z 173 [MH^+]. The observed chemical shifts are in accordance with the literature values.[70]

Decyl decanoate



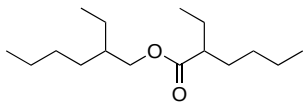
Prepared from decanol. Purified by DCVC, eluting from heptane to ethyl acetate, 2 % increments, to yield the product as a slightly yellow oil in 81 % yield (GC yield: 86 %). ^{1}H-NMR(300 MHz, $CDCl_3$) δ 4.04 (t, J = 6.7 Hz, 2H), 2.27 (t, J = 7.5 Hz, 2H), 1.66–1.53 (m, 4H), 1.25 (m, 26H), 0.86 (t, J = 6.6 Hz, 6H). ^{13}C-NMR(75 MHz, $CDCl_3$) δ 174.1, 64.5, 34.5, 32.0, 32.0, 29.7, 29.7, 29.6, 29.5, 29.4, 29.4, 29.4, 29.3, 28.8, 26.1, 25.2, 22.8, 22.8, 14.2, 14.2. MS: m/z 312 [M^+]. The observed ^{1}H chemical shifts are in accordance with the literature values.[71]

Undecyl undecanoate



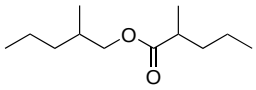
Prepared from undecanol. Purified by DCVC, eluting from heptane to ethyl acetate, 2 % increments, to yield the product as a slightly yellow oil in 76 % yield (GC yield: 84 %). ^{1}H-NMR(300 MHz, $CDCl_3$) δ 4.04 (t, J = 6.7 Hz, 2H), 2.27 (t, J = 7.5 Hz, 2H), 1.69–1.50 (m, 4H), 1.25 (s, 30H), 0.86 (t, J = 6.6 Hz, 6H). ^{13}C-NMR(75 MHz, $CDCl_3$) δ 174.1, 64.5, 34.5, 32.0, 29.8, 29.7, 29.7, 29.7, 29.6, 29.5, 29.5, 29.4, 29.4, 29.3, 28.8, 26.1, 25.2, 22.8, 14.2. MS: m/z 340 [M^+]. The observed ^{1}H chemical shifts are in accordance with the literature values.[72]

2-Ethylhexyl 2-ethylhexanoate



Prepared from 2-ethylhexanol. Purified by DCVC, eluting from pentane to ethyl acetate, 2 % increments, to yield the product as a slightly yellow oil in 64 % yield (GC yield: 63 %). ^{1}H-NMR(300 MHz, $CDCl_3$) δ 3.97 (d, J = 5.7 Hz, 2H), 2.31–2.17 (m, 1H), 1.64–1.10 (m, 17H), 0.95–0.69 (m, 12H). ^{13}C-NMR(75 MHz, $CDCl_3$) δ 176.7, 66.3, 47.7, 38.9, 32.0, 30.6, 29.8, 29.0, 25.7, 24.0, 23.1, 22.8, 14.1, 14.0, 12.0, 11.1. MS: m/z 257 [MH^+]. The observed ^{1}H chemical shifts are in accordance with the literature values.[72]

2-Methylpentyl 2-methylpentanoate

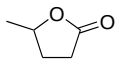


Prepared from 2-methylpentanol. Purified by DCVC, eluting from pentane to ethyl acetate, 2 % increments, to yield the product as a slightly yellow oil in 45 % yield (GC yield: 49 %). ^{1}H-NMR(300 MHz, $CDCl_3$) δ 4.01–3.88 (m, 1H), 3.87–3.79 (m, 1H), 2.42 (dt, J = 13.8, 7.0 Hz, 1H), 1.86–1.70 (m, 1H), 1.70–1.55 (m, 1H), 1.44–1.20 (m, 7H), 1.12 (d, J = 7.0 Hz, 3H), 0.95–0.79 (m, 9H). ^{13}C-NMR(75 MHz, $CDCl_3$) δ 177.09, 69.17, 39.58, 39.56, 36.12, 35.72, 32.44, 20.53, 20.04, 17.22, 16.98, 16.96, 14.35, 14.06. MS: m/z 201 [MH^+]. The observed chemical shifts are in accordance with the literature values.[73]

Gammabutyrolactone

Prepared from 1,4-butanediol. Purified by DCVC, eluting from heptane to ethyl acetate, 10 % increments, to yield the product as a colorless oil in 71 % yield (GC yield: 86 %). ^{1}H-NMR(300 MHz, $CDCl_3$) δ 4.31 (t, J = 7.0 Hz, 2H), 2.50–2.41 (m, 2H), 2.29–2.17 (m, 2H). ^{13}C-NMR(75 MHz, $CDCl_3$) δ 177.8, 68.6, 27.8, 22.2. MS: m/z 86 [M^+]. The observed chemical shifts are in accordance with the literature values.[74]

Gammavalerolactone

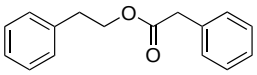


Prepared from 1,4-pentanediol. Purified by DCVC, eluting from heptane to ethyl acetate, 10 % increments, to yield the product as a colorless oil in 78 % yield (GC yield: 82 %). ^{1}H-NMR(300 MHz, $CDCl_3$) δ 4.62–4.50 (m, 1H), 2.50–2.43 (m, 2H), 2.35–2.23 (m, 1H), 1.82–1.68 (m, 1H), 1.32 (d, J = 6.2 Hz, 3H). ^{13}C-NMR(75 MHz, $CDCl_3$) δ 177.2, 77.2, 29.6, 29.0, 21.0. MS: m/z 100 [M^+]. The observed chemical shifts are in accordance with the literature values.[74]

Deltavalerolactone

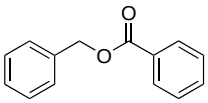
Prepared from 1,5-pentanediol. Purified by DCVC, eluting from heptane to ethyl acetate, 10 % increments, to yield the product as a colorless oil in 61 % yield (GC yield: 63 %). ^{1}H-NMR(300 MHz, $CDCl_3$) δ 4.21 (t, J = 5.9 Hz, 2H), 2.42 (t, J = 7.0 Hz, 2H), 1.88–1.65 (m, 4H). ^{13}C-NMR(75 MHz, $CDCl_3$) δ 171.3, 69.3, 29.6, 22.1, 18.8. MS: m/z 100 [M^+]. The observed chemical shifts are in accordance with the literature values.[74]

Phenethyl 2-phenylacetate



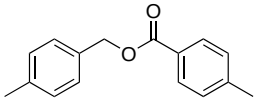
Prepared from 2-phenylethanol. Purified by DCVC, eluting from heptane to ethyl acetate, 2 % increments, to yield the product as a slightly yellow oil in 48 % yield (GC yield: 52 %). ^{1}H-NMR(300 MHz, $CDCl_3$) δ 7.45–7.16 (m, 10H), 4.36 (t, J = 7.0 Hz, 2H), 3.65 (s, 2H), 2.96 (t, J = 7.0 Hz, 2H). ^{13}C-NMR(75 MHz, $CDCl_3$) δ 171.6, 137.8, 134.1, 129.4, 129.0, 128.6, 128.5, 127.1, 126.6, 65.4, 41.5, 35.1. The observed chemical shifts are in accordance with the literature values.[26]

Benzyl benzoate



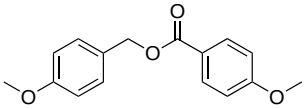
Prepared from benzyl alcohol. Purified by DCVC, eluting from heptane to ethyl acetate, 2 % increments, to yield the product as a slightly yellow oil in 31 % yield (GC yield: 27 %). ^{1}H-NMR(300 MHz, $CDCl_3$) δ 8.16–8.09 (m, 2H), 7.61–7.54 (m, 1H), 7.52–7.33 (m, 7H), 5.40 (s, 2H). ^{13}C-NMR(75 MHz, $CDCl_3$) δ 166.5, 136.1, 133.1, 130.2, 129.8, 128.7, 128.4, 128.3, 128.2, 66.7. MS: m/z 212 [M^+]. The observed chemical shifts are in accordance with the literature values.[75]

4-Methylbenzyl 4-methylbenzoate



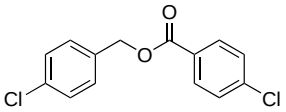
Prepared from 4-methylbenzyl alcohol. Purified by DCVC, eluting from heptane to ethyl acetate, 2 % increments, to yield the product as a slightly yellow oil in 24 % yield. ^{1}H-NMR(300 MHz, $CDCl_3$) δ 7.97 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 5.32 (s, 2H), 2.41 (s, 3H), 2.37 (s, 3H). ^{13}C-NMR(75 MHz, $CDCl_3$) δ 166.7, 143.8, 138.1, 133.3, 129.8, 129.4, 129.2, 128.4, 127.6, 66.6, 21.8, 21.3. MS: m/z 240 [M^+]. The observed chemical shifts are in accordance with the literature values.[63]

4-Methoxybenzyl 4-methoxybenzoate



Prepared from 4-methoxybenzyl alcohol. Purified by DCVC, eluting from heptane to ethyl acetate, 2 % increments, to yield the product as a colorless oil in 19 % yield. ^{1}H-NMR(300 MHz, $CDCl_3$) δ 8.02 (d, J = 9.0 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 3.4 Hz, 2H), 6.89 (d, J = 3.6 Hz, 2H), 5.27 (s, 2H), 3.84 (s, 3H), 3.81 (s, 3H). ^{13}C-NMR(75 MHz, $CDCl_3$) δ 166.4, 163.5, 159.7, 131.8, 130.1, 128.5, 122.8, 114.0, 113.7, 66.4, 55.5, 55.4. MS: m/z 272 [M^+]. The observed chemical shifts are in accordance with the literature values.[76]

4-Chlorobenzyl 4-chlorobenzoate



Prepared from 4-chlorobenzyl alcohol. Purified by DCVC, eluting from heptane to ethyl acetate, 2 % increments, to yield the product as a pale yellow solid in 45 % yield. ^{1}H-NMR(400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.7 Hz, 2H), 7.39 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 2.6 Hz, 4H), 5.30 (s, 2H). ^{13}C-NMR(101 MHz, $CDCl_3$) δ 165.32, 139.53, 134.61, 134.20, 130.97, 129.55, 128.74, 128.68, 128.26, 66.00. MS: m/z 280 [M^+], 139 [$ClPhCO^+$], 125 [$ClPhCH_2{}^+$]. The observed chemical shifts are in accordance with the literature values.[77]

CHAPTER 3

Synthesis of Anti Zigzag-[5]-phenylene

This chapter describes the synthesis and characterization of Anti Zigzag-[5]-phenylene, a hitherto unknown member of the family of [5]-phenylenes. The compound was synthesized in ten steps from commercially available 1,2-dibromobenzene with an overall yield of 0.5 %. The identity of the compound was subsequently confirmed by HRMS and proton NMR.

3.1 Introduction

The [N]-phenylenes are a compound class consisting of alternating benzene and cyclobutadiene units. The N is the 'family name' and designates the number of benzene rings present in the phenylene. When more than two benzene rings are present, two different modes of connectivity becomes possible: Linear and angular. With more than three benzene rings these two modes of connectivity can be combined in an ever increasing amount of different topologies: The more benzene rings, the more topologies become available, and thus the number of family members increases exponentially with increasing N: From two [3]-phenylenes, to five [4]-phenylenes, to twelve [5]-phenylenes and so on.

The members of the [3]- and [4]-phenylene families have all been synthesized, but the family of [5]-phenylenes still have a few prodigal sons, that must be synthesized before the family is complete. One of these is the anti-zigzag-[5]-phenylene, the second structure in figure 3.1. It is closely related to the

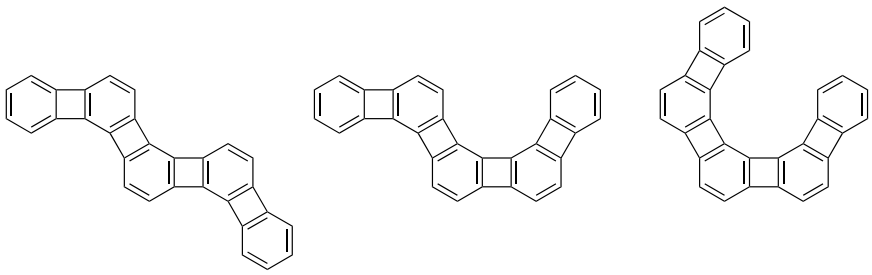


Figure 3.1: The three [5]-phenylenes that have only angular fusions. From left to right: Zigzag-[5]-phenylene, anti-zigzag-[5]-phenylene and angular-[5]-phenylene.

zigzag-[5]-phenylene, the structure furthest to the left, but has the last benzene ring connected in the opposite direction, hence the 'anti'-prefix. It is one of just three [5]-phenylenes to have only angular fusions between the rings, the other two being the angular- and zigzag-[5]-phenylene. The three all-angular [5]-phenylenes are shown in figure 3.1. Phenylenes with angular fusions are in general more stable than their linear relatives, and the anti-zigzag-[5]-phenylene is expected to be among the most stable in the family of [5]-phenylenes, based on DFT calculations.[78]

This unique combination of aromatic and antiaromatic rings in the same molecule, which is inherent to the phenylenes, poses some very interesting structures for the study of aromaticity. For this reason, as well as for the mere achievement of completing the whole set of [5]-phenylenes, the synthesis of this particular molecule is desirable.

3.1.1 Notes on aromaticity

The concept of aromaticity is a difficult matter to discuss and even more so to define. There are many different definitions, depending on who you ask, and some people question whether it is possible to define aromaticity at all.[79] The discussion has its roots all the way back to Faradays discovery of benzene in 1825.[80] Before then the term aromatic was applied to compounds on account of the smell (which makes sense etymologically: The word *aromatic* originates from the ancient greek word $\alpha\rho\omega\mu\alpha$ [arōma], meaning seasoning, spicy and/or fragrant smell), but with the discovery of the unusual stability of benzene the term gradually became associated with something else. Through the years a wide array of different definitions have been presented, based on structure, chemical properties, magnetic- and energetic criteria.

Structure vs. reactivity In 1865 Kekulé published a structure for benzene, later to be known as "The Kekulé Structure".[81] He suggested that aromatic compounds be defined as those compounds which has a core of six or at least six carbon atoms, that has a higher C:H ratio than its hydrocarbon analogue, and which even upon chemical transformation into something else retains that C6 core.[82] In other words, benzene and its derivatives. By these publications he unknowingly started what is still, 150 years later, an ongoing discussion about how best to define aromaticity. The year after Kekulé suggested his definition based on the benzene structure, Erlenmeyer proposed a divergent definition. He agreed with Kekulés proposed structure, but found the definition of aromaticity based on the C6 core to be random, and claimed that if the term was to have any scientific meaning it must be based on the chemical reactivity of the compounds rather than their structure.[83]

The structure and reactivity criteria do not go well hand in hand, as some compounds that would be defined as being aromatic by structural criteria, do not react like aromatic compounds and vice versa. An example is anthracene (figure 3.2) that prefers addition to substitution and undergoes Diels-Alder reactions, or fullerene (figure 3.2) that can not undergo substitution reactions at all.[84] Another problem is that defining something by its properties leads to a kind of circular argument (a logical fallacy): "These compounds, that we call aromatic, exhibit certain properties that we define as being the aromatic properties. Because these compounds exhibit aromatic properties they are aromatic." In other words, in order to define aromaticity by reactivity one needs to decide beforehand what compounds should be considered aromatic. When speaking of reactivity the definition becomes quite relative, as some compounds can be more or less reactive than others, whereas structural components are either present or absent in a molecule, inherently making this way of defining aromaticity more consistent.[85] Nowadays, the structural definition of aromaticity is usually one of equal bond lengts as a consequence of electron delocalization in the ring. Again the criterion works very well for 'classic' aromatic molecules like benzene and its derivatives, but larger aromatic systems like phenanthrene and anthracene (figure 3.2) exhibit quite significant bond length varations, while at the same time e.g. allylic groups have equal bond lengths without being aromatic.[84]

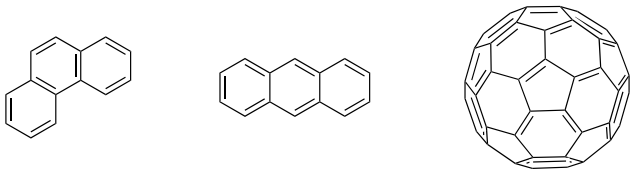


Figure 3.2: From left to right: Phenanthrene, anthracene and C_{60} fullerene.

Magnetic properties Another way of looking at aromatic compounds is in terms of their magnetic properties: Chemical shifts and magnetic susceptibility. The basic principle is that the delocalized π-electrons in the ring create a diamagnetic ring current when the molecule is subjected to an external magnetic field. In other words, the presence of such an induced diamagnetic ring current indicates aromaticity. The ring current shields the area above and below the ring and deshields the area around the 'equator' of the ring, causing the chemical shifts of the former to be at a very high field and the chemical shift of the protons attached to the C6 core to move to a much lower field than is the case for protons on regular double bonds. The problem with using chemical shifts for defining for aromaticity is that they are not uniquely associated with aromatic compounds. One example is acidic protons that are also highly deshielded and thus have chemical shifts at a very low field.[79]

Another magnetic property of aromatic compounds is their anisotropic magnetic susceptibility. Anisotropic means directionally dependant and magnetic susceptibility is a measure for the degree of magnetization a compound exhibits in response to an applied magnetic field. The anisotropic magnetic susceptibility of a compound is thus the spatial dependence of the degree of magnetization in response to the applied magnetic field, which is very high for aromatic compounds, meaning that aromatic compounds are magnetized to a very different extent depending on whether the equator of the compound is aligned with or orthogonal to the magnetic field. Obviously, this property only applies to compounds which are more or less planar, or at least have two different spatial orientations, and thus cannot be used as a criterion when looking at spherical compounds like fullerenes.[84] In addition hereto anisotropic magnetic susceptibility is also a relative property, meaning that some kind of reference has to be set, making it less than ideal as a criterion by which to define something.

The NICS (Nucleus Independent Chemical Shift) value of a molecule is a theoretical chemical shift, measured at any given point in space relative to a molecule, but typically the point at 1Å above the center of the ring is chosen. For aromatic molecules this point is very shielded and the chemical shift is negative ($NICS(1)_{benzene}$ = -12.5), for antiaromatic molecules the opposite is true ($NICS(1)_{cyclobutadiene}$ = 15.1). The NICS values are well suited to define aromaticity, as only molecules with diamagnetic ring currents have such low chemical shifts, but the method suffers the great disadvantage of being purely theoretical and so it cannot be measured, only calculated.[79]

Energetic criteria Yet another property of aromatic compounds is their relative stability. Benzene has a much lower energy of formation compared to similar olefinic and/or cyclic compounds, and the heat of hydrogenation is

much lower too, indicating the stability the molecule gains by being aromatic. The paramount problem with these energetic criteria is that they are all relative properties, and thus vary a lot depending on the choice of reference system. The perfect reference is hard to come by, as it would be the exact same molecule, only not aromatic. A breakthrough in this regard came with the synthesis of the branched [4]-phenylene in 1986[86] (figure 3.3) as this was the first example of an actual 1,3,5-cyclohexatriene - the perfect reference, if any, for benzene.

The most persistent definition of aromaticity, and the one that is provided by all the textbooks, is based on Hückels rule from 1931.[87] It states that a monocircular, planar molecule with 4n+2 π-electrons in a conjugated array (n being zero or a positive integer) is aromatic, while a similar molecule with 4n π-electrons is antiaromatic. An aromatic molecule exhibits higher stability than would have been expected from the contributing components, whereas an antiaromatic molecule exhibits the opposite. Hückel explains the origin of this by applying quantum mechanical calculations to the σ- and π-components of the molecules, and arrives at the conclusion that the delocalization of the π-electrons is the cause of the observed stability of benzene: The more delocalized the π-electrons, the more stable the system. More recent research claims that this is a false conclusion, as a π-system is actually more stable when localized.[88] The delocalization of the π-electrons in benzene is thus a consequence of the symmetry of the σ-system, and not the other way around.[79]

Hückels rule provides a rule of thumb which is easy to remember, but it is only applicable to a very narrow range of compounds, since they have to be both monocyclic and planar. Thus, we cannot really use it to look at more 'unusual' molecules - like for instance phenylenes.

In the absence of one single irrefutable definition of aromaticity we will have to make do with the most commonly accepted definitions and for the remainder of the chapter we shall consider aromatic compounds as those that meets Hückels criteria, as far as monocyclic compounds are concerned, and which to a higher or lesser extent exhibit the energetic, magnetic and chemical properties associated with benzene.

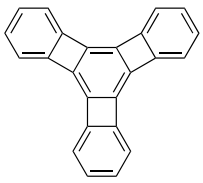


Figure 3.3: The branched [4]-phenylene, named the "starburst phenylene" was synthesized in 1986 and was the first example of an actual 1,3,5-cyclohexatriene.

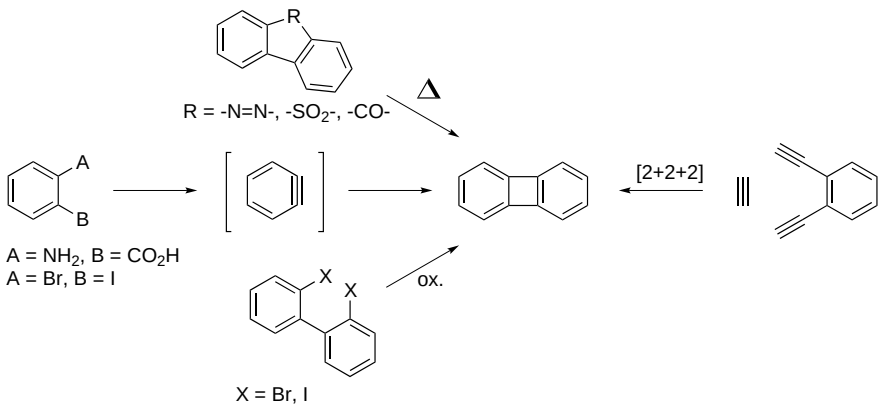


Figure 3.4: Different ways to synthesize biphenylene. On the left, from top to bottom: a) Extrusion of small molecules from a bridged biaryl, b) dimerization of arynes, c) dehalogenation of 2,2'-dihalogenated biphenyls. On the right, the Co-mediated [2+2+2] cycloaddition.

3.1.2 Biphenylene: Preparation and properties

The smallest possible phenylene is biphenylene, which was first synthesized by Lothrop in 1941.[89] Being an intriguing molecule its synthesis had been pursued for many years, the earliest recorded attempt in 1893 by Hosaeus,[90] but nobody succeeded until Lothrop applied cuprous oxide to 2,2'-dibromobiphenyl. Later biphenylene has been successfully synthesized in a multitude of ways, outlined in figure 3.4. The various methods can be classified in three different categories as either a) extrusion of a small molecule from a bridged biaryl, b) dimerization of arynes or c) dehalogenation of 2,2'-dihalogenated biphenyls.[91] A fourth method, that does not fall into any of these categories, were developed in the Vollhardt group, and utilizes a cobalt complex to mediate a [2+2+2] cycloaddition of bis-trimethylsilylethylene and 1,2-diacetylbenzene.[92]

In theory the electronic structure of biphenylene should be an average of the five possible resonance structures, shown in figure 3.5, resulting in equal bond lengths like in benzene, but the X-ray structure of biphenylene shows that this is not so.[93] The bonds between the two aryl rings are comparable to single bonds and the bonds in the benzenoid rings are of alternating length, which gives

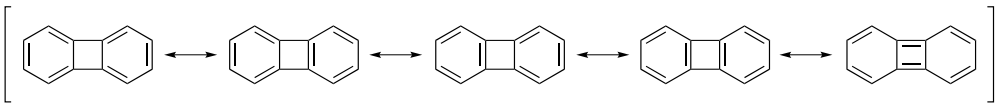


Figure 3.5: The five possible resonance structures for biphenylene.

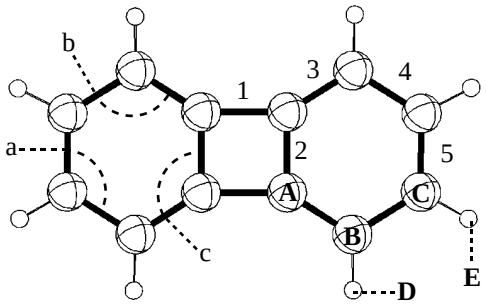


Figure 3.6: The X-ray crystal structure of biphenylene. The bond lengths are: 1: 1.514 Å; 2: 1.426 Å; 3: 1.372 Å; 4: 1.423 Å; 5: 1.385 Å. The bond angles are: a: 122.2°; b: 115.2°; c: 122.6°. The chemical shifts are: A: 151.2 ppm; B: 128.2 ppm; C: 117.3 ppm; D: 6.73 ppm; E: 6.62 ppm.

a structure more resembling two cyclohexatrienes fused with a cyclobutane, than two benzenes fused with a cyclobutadiene. This means that the resonance structures are not evenly represented, but rather the structure furthest to the left dominates, while the structure furthest to the right hardly is present at all. In other words, the double bonds are localized in a way that minimizes the cyclobutadienoid character of the molecule, thus reducing the antiaromaticity of the molecule even at the cost of reducing the aromaticity of the benzenoid parts of the molecule. This trend is also evident in the chemical shifts of biphenylene. Where benzene has a ^{1}H chemical shift of 7.34 ppm in deuterated chloroform, the chemical shifts of biphenylene are moved upfield, to multiplets at 6.73 and 6.62 ppm.[94] The proton and carbon chemical shifts are given on the X-ray structure in figure 3.6.

Despite the (partly) localized double bonds and the upshifted chemical shifts, biphenylene can still be considered an aromatic molecule on the grounds of its reactivity. It reacts with electrophiles by aromatic electrophilic sub-

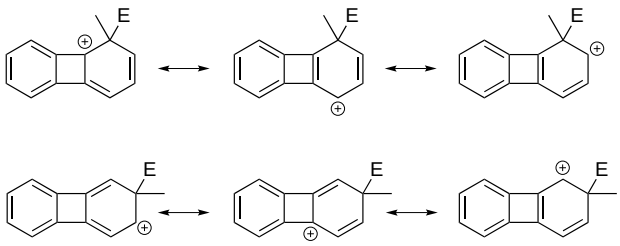


Figure 3.7: Available resonance structures for the Wheland intermediates for substitution at the α-position (top) and β-position (bottom) of biphenylene.

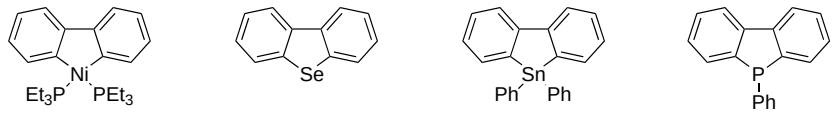


Figure 3.8: Four examples of organometallic products resulting from the reaction of biphenylene with inorganic compounds.

stitution, not by addition, but the substitutions take place preferably in the β-position of biphenylene and not in the α-position like for example naphthalene.[95] This may be explained by comparing the available resonance forms for the Wheland intermediates of the α- and β-substitution, respectively, see figure 3.7. Here it is clear that for the α-substitution two of the contributing resonance forms have a double bond placed in the four-membered ring, which is only the case for one of the contributing resonance forms for the β-substitution. These forms are unfavorable on account of their high strain[96] as well as the fact that they are cyclobutadienoid species and therefore of considerably higher energy than the resonance forms that have the double bonds exocyclic to the four-membered ring.[97] Another explanation is offered by considering the hybridization of the carbon atoms of biphenylene. The strain of the four-membered ring causes a rehybridization of the bridgehead carbon from three equal sp^2 orbitals, to two orbitals of higher p-character and one orbital of higher s-character, used for the bond to the α-carbon. Being bound to an orbital of higher electronegativity causes the α-carbon to have enhanced acidity as well as reduced reactivity towards electrophilic substitution.[98]

Biphenylene does not react as a diene in Diels-Alder reactions with maleic anhydride and tetracyanoethylene,[95] but it does react as a dienophile with very electron deficient dienes like tetrachloro- or tetrafluorobenzyne to form monoadducts; a reaction that has also been reported for other aromatic compounds.[99] It can be hydrogenated under mild conditions, e.g. over Raney nickel at room temperature, to form biphenyl, but only under more vigorous conditions are double bonds in the aromatic rings reduced.[100] Pyrolysis results in the formation of tetraphenylene, via the biphenyl diradical.[101] Biphenylene reacts with a wide array of inorganic compounds to form organometallic species like the ones shown in figure 3.8.[102]

3.1.3 [N]-Phenylene topologies

The first successful synthesis of a higher order of phenylene than biphenylene was published in 1978 by Barton and coworkers. They reported the synthesis of one of the two possible [3]-phenylenes, i.e. the so-called angular-[3]-phenylene, by thermal extrusion of nitrogen from benzo[1,2-c:4,3-c']dicinnoline.[103] The me-

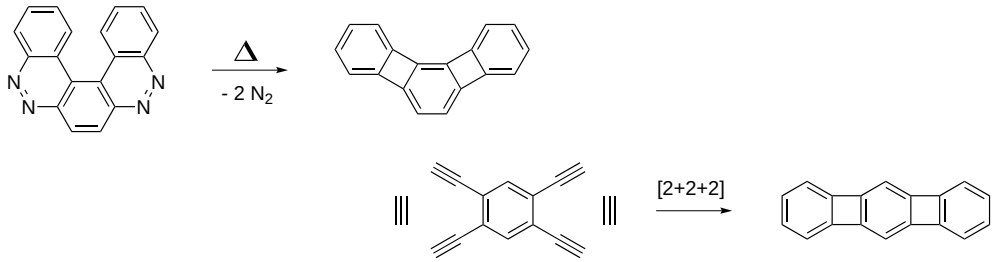


Figure 3.9: On the left the synthesis of angular-[3]-phenylene by thermal extrusion of nitrogen from benzo[1,2-c:4,3-c']dicinnoline by Barton and coworkers. On the right the synthesis of linear-[3]-phenylene by the cobalt mediated [2+2+2] cycloaddition of two acetylenes to 1,2,4,5-tetraethynylbenzene by Vollhardt and coworkers.

thod was also attempted to be used for the synthesis of the linear-[3]-phenylene but was not suitable and it was another seven years before the other isomer of [3]-phenylene was synthesized. This was done by Vollhardt and coworkers, by the application of the cobalt mediated [2+2+2] cycloaddition of acetylenes to di- and tetraethynylbenzenes as an iterative method for preparing linear phenylenes.[92] This method was subsequently utilized for a more efficient synthesis of angular-[3]-phenylene.[104] Both methods are illustrated in figure 3.9.

When comparing the structural and magnetic properties of the two species it becomes clear that topology plays an important role. For the angular [3]-phenylene the localization of the π-electrons in the terminal benzene rings is decreased compared to biphenylene, but at the same time the localization of π-electrons in the central six-membered rings increases dramatically. It seems likely that the inner ring adopts a cyclohexatriene conformation to keep the π-eletrons out of the four-membered rings, thus allowing the terminal rings to relax and adopt a more benzene-like structure. For the linear [3]-phenylene the picture is turned around and the localization of the π-electrons in the terminal benzene rings is increased compared to biphenylene. The central ring in the linear species cannot exist as a cyclohexatriene structure for symmetry reasons, and instead adopts a bisallylic conformation, with the fused bonds between the rings being longer and the rest of the bonds being shorter.[105]

In the years following the synthesis of the linear-[3]-phenylene, the family of [N]-phenylenes was extended extensively by the Vollhardt group, by applying the cobalt mediated [2+2+2] cyclization to a wide variety of acetylenic compounds, proving it to be a very efficient and trustworthy methodology for the synthesis of phenylenes in particular and aromatic compounds in general. The family of [4]-phenylenes have all been synthesized and feature a bent,[106] a zigzag[107] and a branched[86] phenylene topology, in addition to the linear[108] and angular[109] ones, shown in figure 3.10.

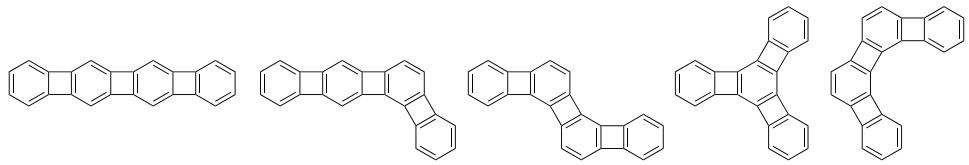


Figure 3.10: The family of [4]-phenylenes. From left to right: Linear-[4]-phenylene (1986), bent-[4]-phenylene (2002), zigzag-[4]-phenylene (1999), branched-[4]-phenylene (1986), angular-[4]-phenylene (1992).

The much more extensive family of [5]-phenylenes have a total of twelve different isomers. Most of these have already been synthesized,[107,109,110,78] but five of them are still missing (molecules marked in red in figure 3.11).

The group of angular-[N]-phenylenes have been expanded further; up to and including the angular-[9]-phenylene.[111] The angular phenylenes adopt a helical conformation from six or more benzene rings and therefore have been dubbed helical-[N]-phenylenes or heliphenes. The x-ray structures of the angular [5]–, [6]– and [7]-phenylenes are shown in figure 3.12, where it is clear to see the adoption of the helical conformation.

Many attempts have been made to synthesize the circular-[6]-phenylene but so far all of them have been unfruitful.[105] The compound has been named anti-kekuléne due to its similarity to the PAH kekuléne, which contains an equal number of rings, though all of them are benzenoid in the latter. Both

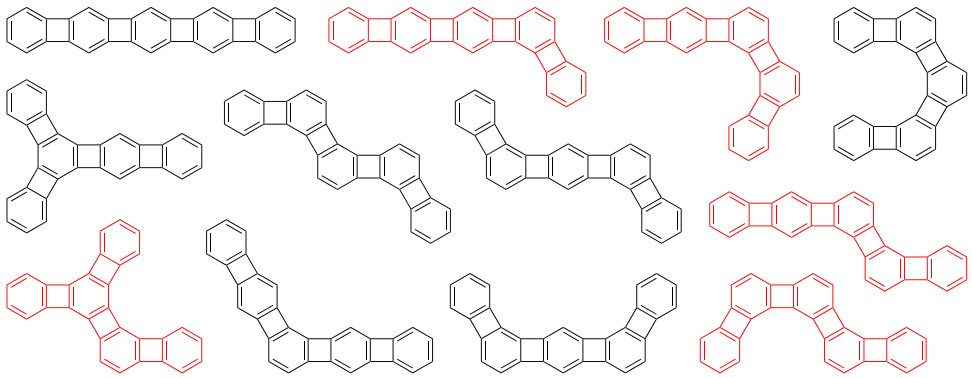


Figure 3.11: The family of [5]-phenylenes. Black compounds: Top row from left to right: Linear-[5]-phenylene (1987), angular-[5]-phenylene (1992). Middle row from left to right: Branched-[5]-phenylene (1995), zigzag-[5]-phenylene (1999), anti-doublebent-[5]-phenylenes (2004). Bottom row from left to right: Bent-[5]-phenylene (2005), syn-doublebent-[5]-phenylene (2004). The red compounds have not yet been synthesized; the compound at the bottom right is the target molecule anti zigzag-[5]-phenylene.

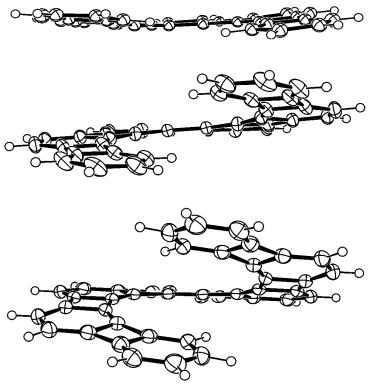


Figure 3.12: The X-ray structures of the angular [5]-, [6]- and [7]-phenylenes, showing clearly the helical conformation the compounds adopt when reaching a certain size.

compounds are shown in figure 3.13. The anti-kekuléne is considered the holy grail of the phenylenes. This compound would be the ultimate combination of an aromatic and an anti-aromatic compound: If the double bonds were to localize outside of the four-membered rings, as would be expected based on the behavior of the other angular phenylenes, it would result in a electronic structure as drawn in figure 3.13. This opens up for the possibility of a so-called super-delocalization in both the inner and outer loops of the compound, but both of these being antiaromatic by Hückels definition, with a circular array of 12 and 24 π-electrons, respectively. The fact that all the attempts to synthesize this compound so far has been unfruitful may serve as a testimony to how unstable such a super-anti-aromatic structure might really be.

When comparing the physical properties of all these phenylenes certain trends become apparent. The pattern of π-bond localization in the central benzene ring and delocalization in the terminal benzene rings that was observed for the angular-[3]-phenylene is repeated in the other phenylenes with angular connections. This trend causes these phenylenes to be in general more

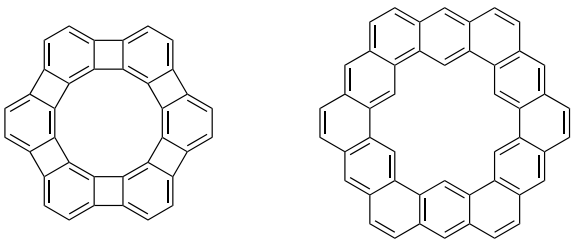


Figure 3.13: To the left: The circular [6]-phenylene, dubbed anti-kekuléne. To the right: The PAH kekuléne.

aromatic and thus more stable than their linear counterparts. Most stable of them all are the branched isomers. The branched-[4]-phenylene, also called the starburst phenylene, experiences 97 % bond lenght alternation in the central ring, but only 20 % in the outer rings, and is the first reported example of what must be considered a 1,3,5-cyclohexatriene.[86]

Apart from the bond length alternation, which can be seen from X-ray structures of the compounds in question, the trend also manifests itself in the chemical shifts of the phenylenes, as well as in the calculated NICS values. Where the proton chemical shifts of biphenylene was moved 0.68-0.78 ppm upfield as compared to benzene (from 7.34 to 6.66-6.56), the proton chemical shifts in the central ring of angular-[3]-phenylene are moved an additional 0.38–0.48 ppm upfield as compared to biphenylene. On the contrary, the protons on the terminal rings of branched-[4]-phenylene have chemical shifts that are almost the same as in benzene (7.31 and 7.24). The NICS values from theoretical calculations also supports this tendency, and even provides a guideline for what to expect from the phenylenes that have not yet been synthesized, in terms of aromaticity and stability.

3.2 Synthesis and mechanisms

The target molecule for this project was a missing member of the family of [5]-phenylenes. The retrosynthetic analysis of the desired phenylene is shown in figure 3.14. It commences with a disconnection of the [5]-phenylene into a triyne, which can be subjected to a cobalt mediated [2+2+2] cycloaddition to yield the desired product. The triyne is envisioned to arise from a Sonogashira coupling between two similar alkyne substituted biphenylenes. The two biphenylenes can both be synthesized from the same 1,2-disubstituted biphenylene, by selective Sonogashira couplings with orthogonally protected acetylenes.

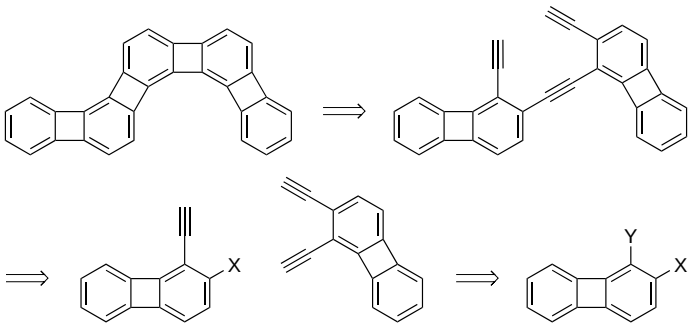


Figure 3.14: Retrosynthetic analysis

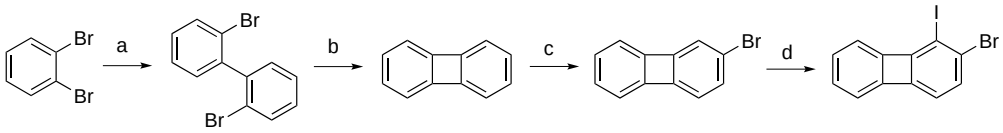


Figure 3.15: The reaction conditions and yield for formation of 2-bromo-1-iodobiphenylene as described in the literature: a) *n*-BuLi, THF, -78 °C, 73 %.[112] b) i. *n*-BuLi, THF, -78 °C. ii. $ZnCl_2$, THF, -50 °C. iii. $CuCl_2$, -78 °C. 80 %.[94] c) NBS, DMF, r.t., 93 %.[113] d) i. LDA, THF, -78 °C. ii. I_2, -78 °C, r.t. 76 %.[115]

3.2.1 Starting material

The starting point of this synthetic strategy is 2-bromo-1-iodobiphenylene, a known compound, which can be made in four steps from 1,2-dibromobenzene, following procedures described in the literature, see figure 3.15. The 2-bromo-1-iodo substitution pattern makes it possible to differentiate between the two positions on biphenylene: Iodine is generally more reactive than bromine in Sonogashira couplings, and will react first, but the 2-position in biphenylene is the more reactive one, and thus the bromine in this position is still reactive enough to be coupled with an acetylene under slightly harsher reaction conditions.

The first step on this route is formation of 2,2'-dibromobiphenyl from 1,2-dibromobenzene with *n*-butyl lithium in THF. According to a study of the mechanism by Leroux and coworkers from 2007 the reaction proceeds via a halogen metal exchange to yield *o*-bromophenyllithium, which *β*-eliminates to give benzyne as a very reactive intermediate. Benzyne reacts with another molecule of *o*-bromophenyl lithium to give a 2-bromobiphenyl lithium intermediate, which is then stabilized by *in situ* transfer of bromine from a molecule of unreacted 1,2-dibromobenzene, see the mechanism in figure 3.16.[116] Gilmans procedure from 1957 was followed to yield 2,2'-dibromobiphenyl as off-white crystals in 68 % yield.[112]

2,2'-Dibromobiphenyl was then transformed into biphenylene (figure 3.17), following a procedure published by Iyoda and coworkers in 2001.[94] This reac-

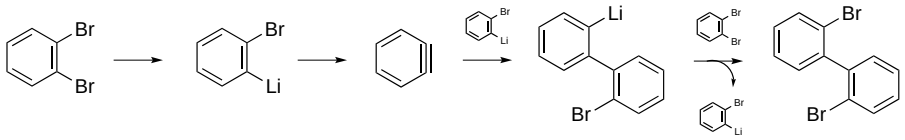


Figure 3.16: The mechanism for formation of 2,2'-dibromobiphenyl from 1,2-dibromobenzene proposed by Leroux and coworkers.[116]

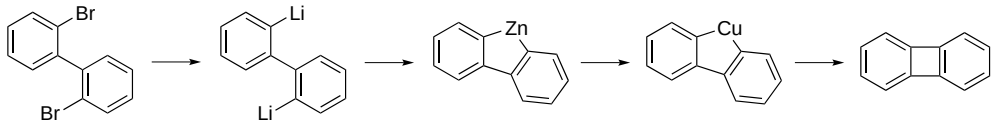


Figure 3.17: The mechanism for formation of biphenylene from 2,2'-dibromobiphenyl, by Iyodas procedure.

tion happens in three steps: First, a halogen metal exchange of bromine for lithium with *n*-butyl lithium in THF, then transmetallation of the resulting dilithium intermediate to a bridged zinc-intermediate with $ZnCl_2$ followed by another transmetallation to a bridged oganocopper species with $CuCl_2$, which was then finally reductively eliminated to give biphenylene. The crude product was crystallized from ether and methanol to give the pure product as colorless needle shaped crystals in 41 % yield. The mother liquor from several batches of the reaction could be combined and crystallized again to give more product, making the actual yield from each reaction slightly higher than the 41 % obtained.

The Iyoda procedure is more or less the same as the one published by Radius and coworkers in 2005,[117] where biphenyl is transformed directly to biphenylene following these steps. Here the initial deprotonation happens in the ortho-positions of the biphenyl on account of inductive and solvating effects of the phenyl ring. The two consecutive transmetallations, first with zinc and then with copper, and then the final reductive elimination, are the same as in the Iyoda procedure. An attempt was made to synthesize biphenylene following this procedure instead, but it was unfruitful and gave only byproduct contaminated biphenyl after workup. Due to the limited time at hand, no further attempts were made to make this procedure work, as the Iyoda procedure was effective and less time consuming.

Biphenylene was brominated in the 2-position with 1 equivalent of NBS in DMF. After stirring for 1 day at room temperature the reaction mixture was subjected to a standard aqueous workup procedure and the crude product purified on a short silica column, eluting with petroleum ether, to give 2-bromobiphenylene in 70 % yield.

2-bromobiphenylene was ortho-lithiated regioselectively with lithium diisopropylamide in THF and subsequently iodinated in that same position in 65 % yield, utilizing a one-pot procedure developed in the Vollhardt group.[115] The product after workup was contaminated with starting material, but it was decided to use the compound mixture directly in the next step, as the product mixture resulting from this reaction proved to be easy to separate by flash chromatography.

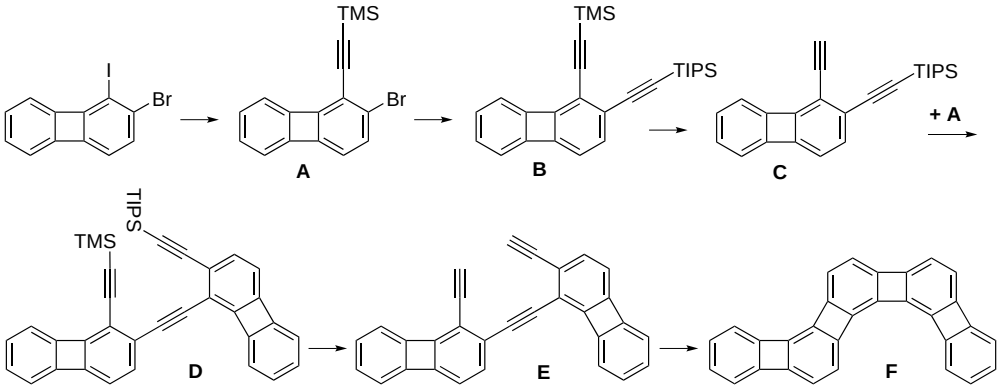


Figure 3.18: From 2-bromo-1-iodobiphenylene three Sonogashira reactions and a cobalt catalyzed [2+2+2] cycloaddition leads to the desired [5]-phenylene.

From 2-bromo-1-iodobiphenylene the synthesis of anti zigzag-[5]-phenylene **F** should be possible in 6 steps, as outlined in the strategy in figure 3.18. Two consecutive Sonogashira couplings with orthogonally protected acetylenes give first the compound **A** and then the compound **B**. The alkyne group in the 1-position of **B** is selectively deprotected to give **C** and a third Sonogashira coupling with compound **A** yields the diprotected triyne intermediate **D**. **D** is fully deprotected to give **E**, which is then subjected to a cobalt catalyzed [2+2+2] cycloaddition to yield the desired phenylene **F**.

3.2.2 Sonogashira couplings

Background The Sonogashira coupling was first reported by Kenkichi Sonogashira and coworkers in 1975, in a paper describing the substitution of acetylenic hydrogens with iodoarenes, bromoalkenes or bromopyridines under mild conditions, namely in diethylamine at room temperature utilizing $PdCl_2(PPh_3)_2$ as catalyst and CuI as co-catalyst.[8] The reaction is related to the Heck coupling, which had been reported a couple of years earlier and employs a similar catalyst to couple unsaturated halides with alkenes, although under much harsher conditions.[118] Both Heck[119] and Cassar[120] had earlier reported that it was possible to perform these kinds of couplings with a palladium catalyst like $PdCl_2(PPh_3)_2$ at high temperatures, but Sonogashira greatly improved this finding by combining the catalytically powerful palladium with the known transmetallation reaction between copper and acetylenes, thus allowing the net reaction to proceed at room temperature. The scope of the reaction combined with the mild reaction conditions has made the Sonogashira coupling extremely popular and it is today the most widely employed way to alkynylate aryls and other unsaturated

compounds.[121]

Though the reaction has been known for almost 40 years the exact details of the mechanism are still not completely determined, which is mainly due to difficulties in analyzing the combined action of the two metals present. The overall mechanism though is generally accepted to follow two independant catalytic cycles, namely a palladium and a copper cycle, as illustrated in figure 3.19.[122]

The palladium cycle is fairly well understood and follows the same general steps as other palladium catalyzed coupling reactions. The first step is an oxidative addition of the substrate (R_1-X) to the coordinatively unsaturated 14-electron $Pd(0)L_2$ species, which is formed *in situ* by reduction of the available palladium(II) complex. This step is usually fast. The next step can be viewed as a nucleophilic substitution on palladium by the acetylenic anion (which it would be in the absence of copper) but is more likely a transmetallation between the palladium complex and the acetylenic copper species that arises from the reaction of CuI and the acetylene. The transmetallation step is usually the rate-determining step. This step is followed by a trans/cis isomerization in order to place the substrate and the acetylene in close enough proximity to facilitate the last step, which is a reductive elimination to create the product and regenerate the catalyst. The copper cycle is less well understood, but most likely happens in three steps. First a coordination of copper to the acetylene makes the acetylenic proton more acidic and thus more susceptible to deprotonation by the employed amine, which would otherwise be too weak a base. The deprotonation of the acetylene changes it from a cop-

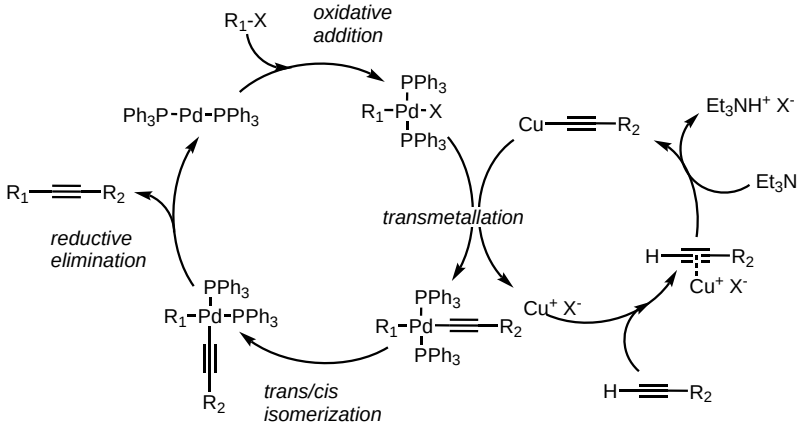


Figure 3.19: The generally accepted mechanism of the Sonogashira coupling. On the left the palladium catalytic cycle and on the right the copper catalytic cycle.

per complex to an organocopper species where the copper is bound directly to the terminal acetylene carbon. This species undergoes a transmetallation with the palladium-substrate-complex from the palladium cycle, forming a copper halide salt. This salt now coordinates to another molecule of the acetylene, thus continuing the catalytic cycle.[123]

While copper makes it possible to perform the coupling reactions under very mild conditions it also suffers from the drawback of making the reactions very air sensitive. In the presence of air and base copper catalyzes the homocoupling of terminal alkynes in what is known as the Glaser-Hay coupling. This is not a big problem if the acetylene to be used is readily available and can be added in great excess, but in the case of synthetically demanding or expensive acetylenes this is not always an option. The extent to which homocoupling of the acetylene happens can be diminished, obviously by keeping the reaction completely free from air, but also by the presence of a reducing atmosphere[124] or by very slow addition of the acetylene,[125] but for practical reasons copper-free procedures are very appealing in many cases. General procedures for copper-free conditions involve using a large excess of base, or even using the base as solvent, running the reaction at higher temperatures and using more reactive substrates. More advanced approaches include the use of ionic liquids as solvent, changing the ligands on palladium, or having palladium on a solid support, among many others. For reviews see[122,123].

Synthetic application The first two alkynylations of the current synthetic strategy were performed using standard Sonogashira reaction conditions, shown in figure 3.20. The first step was a coupling of trimethylsilylacetylene to the 1-position of 2-bromo-1-iodobiphenylene, which was accomplished in Et_3N at 28 °C, with 5 mol % of $PdCl_2(PPh_3)_2$ and 8 mol % of CuI. After stirring for two days, no starting material was present, determined by GC/MS. After a short aqueous workup the crude product was purified by flash chromatography, eluting with petroleum ether, to give compound **A** in 63 % yield.

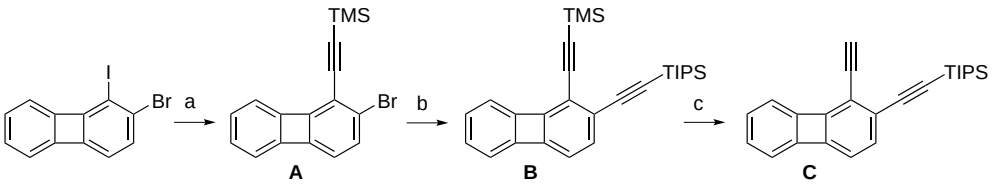


Figure 3.20: a) TMSA (3 eq.), $PdCl_2(PPh_3)_2$ (5 %), CuI (8 %), Et_3N, 28 °C, 2 days, 63 %. b) TIPSA (3 eq.), $PdCl_2(PPh_3)_2$ (8 %), CuI (22 %), piperidine, 50 °C, 1 day, 64 %. c) K_2CO_3, MeOH, Et_2O, r.t., 1 day, 98 %.

Compound **A** was coupled with triisopropylsilylacetylene under slightly harsher conditions to allow the coupling to proceed on the less reactive bromobiphenylene. The coupling took place in piperidine in the presence of 8 mol % of $PdCl_2(PPh_3)_2$ and 22 mol % of CuI. The reaction mixture was heated to 50 °C and left stirring at this temperature until the next day, where no starting material was present as determined by GC/MS. The reaction mixture was subjected to the same work-up procedure as for the previous reaction and the crude product was purified by flash chromatography, eluting with petroleum ether, to give compound **B** in 64 % yield. The TMS-group was removed from compound **B** without affecting the TIPS-group, using K_2CO_3 in methanol. The reaction was stirred at room temperature over night and the crude product mixture was purified by flash chromatography, eluting with a mixture of hexane and DCM (10:1) to yield compound **C** in 98 % yield.

The first Sonogashira coupling is very temperature sensitive. Running the reaction at room temperature resulted in only 48 % yield, while increasing the temperature to 35 °C caused alkynylation at both the 1- and the 2-position of biphenylene. TMS-protected mono- and di-alkynylated biphenylenes (compounds **G**, **H** and **I**, shown in figure 3.21) were synthesized this way, from 2-bromo-1-iodobiphenylene as well as 2-bromobiphenylene and 2,6-dibromobiphenylene impurities present herein. This result emphasizes how the two opposing tendencies, namely the higher reactivity of iodine in Sonogashira couplings versus the higher reactivity on the 2-position of biphenylene, makes the difference in reactivity very subtle indeed, and in the light of this the fact that discrimination between the two positions takes place at all is quite impressive. It also shows, for future experiments, that the second Sonogashira coupling does not need to be run at 50 °C, but can be run at a mere 35 °C.

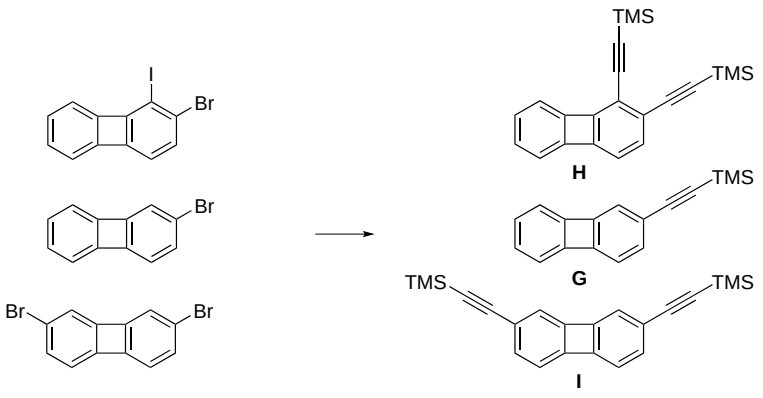


Figure 3.21: Increasing the temperature of the sonogashira reaction to 35 °C causes acetylenic coupling to proceed at both bromine and iodine.

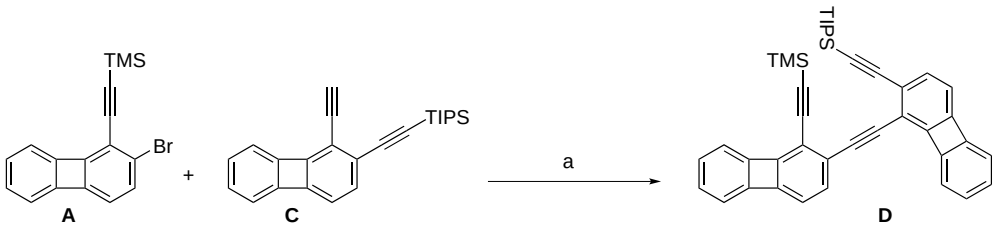


Figure 3.22: a) $PdCl_2(PPh_3)_2$ (10 %), CuI (14 %), Et_3N, THF, 95-97 °C, 2 days, 31 %.

The third Sonogashira coupling in the synthesis (figure 3.22) required a little more care, as the acetylene to be coupled, compound **C**, was the product of seven synthetic steps and thus not available in large enough amounts to add in excess. This meant that the reaction had to be run completely air free in order to avoid the Glaser-Hay coupling as a side-reaction. The reactants, reagents and solvent were mixed in a Schlenk bomb in a glovebox and sealed tightly before transferring it to a regular fumehood and heating the reaction to 95-97 °C for two days. The crude reaction mixture was purified by flash chromatography, eluting with a mixture of hexane and DCM (50:1) to yield compound **D** as an orange-brown solid in 31 %.

3.2.3 Cobalt-catalyzed [2+2+2] cycloaddition

Background In 1866 Berthelot reported that he had observed formation of benzene, among many other products, upon heating acetylene to 400 °C.[126] The harsh reaction conditions and the complex mixture of products made the discovery interesting mainly from a theoretical point of view, with no real synthetic value and further investigation of the reaction lay dormant for over eighty years. In 1948 Reppe discovered that the same reaction could be performed at only 60-70 °C in the presence of $Ni(CO)_2(PPh_3)_2$, forming benzene in 88 % yield.[127] Since then the scope of the reaction has been expanded tremendously and complexes of no less than 17 transition metals (e.g. Co, Pd, Cr, Fe, Ru and Ta among others) have been employed as catalysts in the trimerization of acetylenes and similar compounds.[128]

The trimerization of substituted acetylenes yields substituted benzenes, but low regioselectivity leads to a mixture of isomers in most cases, which limits the method to homotrimerization of symmetric acetylenes.[129] A breakthrough in this regard came in 1974 with the application of α,ω-diynes as substrates for cyclization with acetylenes to form annelated benzenes, utilizing $CpCo(CO)_2$ as catalyst.[130] With the use of diynes the regioselectivity is ensured, and sub-

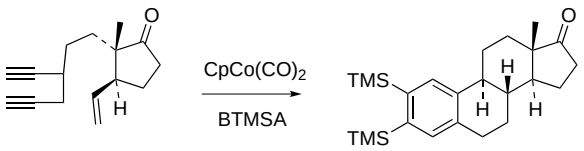


Figure 3.23: A step in the total synthesis of (±)estrone. Five new bonds and the skeleton of the steroid is formed in one step by a cobalt-catalyzed cycloaddition.

stitution of the acetylenes with bulky endgroups like TMS limits the extent of homotrimerization of the acetylene. An impressive example of this kind of reaction is a total synthesis of (±)estrone from 1980, in which five new bonds and the skeleton of the steroid is formed in one step from a monocyclic diyne.[131] The reaction is shown in figure 3.23.

The completely intramolecular [2+2+2] cycloaddition of triynes is the key step in the more than 20 phenylene syntheses published by the Vollhardt group. The most stunning of these is perhaps the synthesis of the helical [7]-, [8]- and [9]-phenylene where a total of nine rings (including six four-membered rings) are constructed from the appropriate nonayne precurser in a single synthetic step.[111] The final step in the synthesis of the helical [7]-phenylene is shown in figure 3.24.

The generally accepted mechanism for the cobalt-catalyzed trimerization of alkynes is shown in figure 3.25. It begins with the displacement of ligands, typically CO, from the cobalt metal, which requires rather high temperatures. This leaves the cobalt coordinatively unsaturated and hence the next step is coordination of two alkynes to cobalt. This is followed by an oxidative addition to give the coordinatively unsaturated d^6 metallacyclopentadiene to which a third alkyne now coordinates. From here the reaction can follow two possible pathways: Either insertion of the alkyne to form a metallacycloheptatriene followed by reductive elimination, or a [2+4] cycloaddition followed by a reductive elimination, to give the same product.[132]

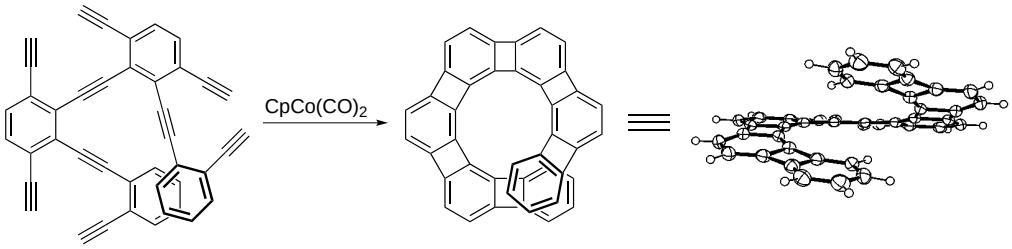


Figure 3.24: The final step in the synthesis of helical [7]-phenylene.

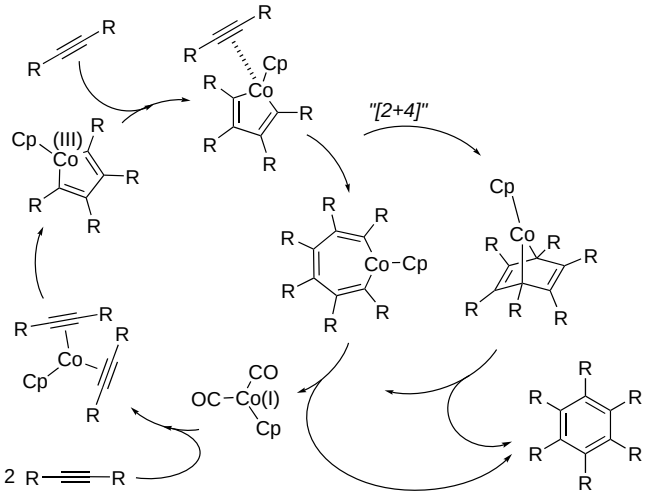


Figure 3.25: The generally accepted mechanism of the cobalt-mediated [2+2+2] cycloaddition.

Synthetic application Compound **D** was deprotected with TBAF in THF and ethanol at room temperature to yield the unprotected triyne **E**. Compound **E** was not isolated as it was anticipated to be very air sensitive. The reaction mixture was subjected to a quick aqueous workup and concentrated in vacuo to yield a yellow slurry, which was immediately placed under N_2 and dissolved in toluene. $CpCo(CO)_2$ was added to the solution and this reaction mixture was added slowly via syringe into refluxing toluene under irradiation during a couple of hours. The reaction was refluxed for another hour under irradiation and then stored at -75 °C under N_2 until the next day, where the volatiles were removed in vacuo and the crude product purified by flash chromatography, eluting with hexane:DCM (10:1) to yield the anti zigzag-[5]-phenylene **F** as a yellow solid. ^{1}H NMR spectra were recorded in both acetone-d_6 and chloroform-d, and shows

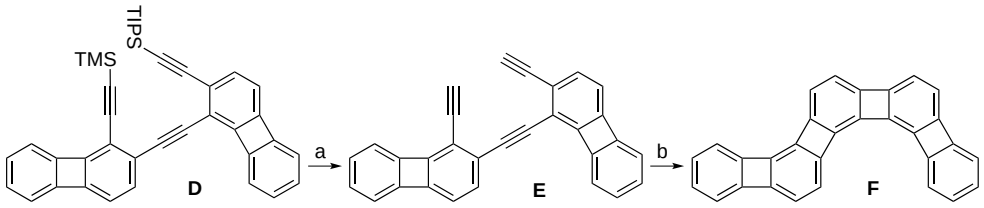


Figure 3.26: Transformation of the diprotected triyne (D) to anti-zigzag-[5]-phenylene (F) over the unprotected triyne (E). a) TBAF, THF, EtOH, r.t., 1 h (not isolated). b) $CpCo(CO)_2$, toluene, Δ, hν , 3 hours, 30 %.

impurities of what looks like a dioctyl phthalate (a plasticizer, probably from the syringe used) in a ratio of 1:1.3, making the isolated yield of the reaction around 30 % over two steps.

3.3 Physical properties of Anti Zigzag-[5]-phenylene

The pure anti zigzag-[5]-phenylene was obtained as a bright yellow crystalline solid, although in minuscule amounts. Low and high resolution mass spectra were recorded and were satisfactory. Proton NMR was recorded both in deuterated acetone and in deuterated chloroform and the assignment of the spectra is discussed in the following section. Unfortunately the solubility of the compound was not high enough to obtain a ^{13}C NMR spectrum from the sample in deuterated acetone, and during the recording of a ^{13}C NMR spectrum in deuterated chloroform the compound decomposed.

It is known from a study of the angular-[4]-phenylene that transformation to the oxidized form **2**, shown in figure 3.27, takes place within 72 hours when storing the compound in chloroform in the presence of air.[115] A similar sensitivity to air is anticipated for the other phenylenes and degradation by air and possible trace amounts of HCl present in the chloroform is expected to be the cause of the decomposition. Due to this unfortunate event no UV- or IR-spectra were recorded and neither was an X-Ray structure obtained.

3.3.1 Assignment of ^{1}H-NMR spectrum

The degree of delocalization of the double bonds in an aromatic ring can be assessed from the C–C bond lengths as observed by X-ray crystallography. From the X-ray structures of a range of different phenylenes the general trend has been detected that the molecules exhibit alternating degrees of localization of the double bonds when moving from one six-membered ring to the next. In the central rings the double bonds become more localized, if symmetry allows it, presumably in order to keep the π-electrons out of the four-membered rings.

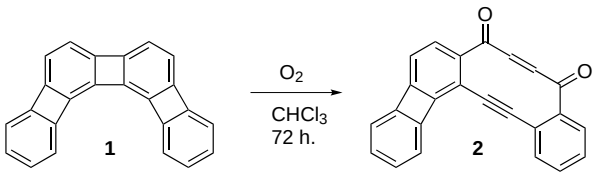


Figure 3.27: In the presence of air the angular-[4]-phenylene **1** oxidizes to compound **2** within 72 hours.[115]

This allows the terminal rings to become more relaxed and their double bonds to delocalize, because the amount of double-bond character this induces in the four-membered rings does not make it antiaromatic when the π-electrons at the subsequent ring-fusion is kept strictly out of it. For the [5]-phenylenes the second and fourth six-membered ring experiences the highest degree of localization, the terminal rings have the most delocalized π-electrons, and the central ring is somewhere in between. This is reflected in the chemical shifts of the protons on the rings in question: The protons on the rings that experience the highest degree of localization have chemical shifts further upfield than the protons on the rings with a lesser extent of localization.[105]

As was mentioned in the introduction the anti zigzag-[5]-phenylene is, at least structurally, somewhere in between the zigzag- and the angular-[5]-phenylene, and the chemical shifts of its protons are expected to be comparable to these, bearing in mind of course that both the zigzag- and the angular isomers are symmetric and thus have a much simpler spectrum than the unsymmetric anti zigzag analogue. The proton NMR spectrums of the two symmetric isomers both show several multiplets (two for the zigzag-, four for the angular isomer) furthest downfield corresponding to the eight protons on the terminal rings; a singlet from the two protons on the central ring upfield from these multiplets and two doublets at almost the same chemical shift (AB system) from the four protons on the second and fourth rings at the highest field. The proton

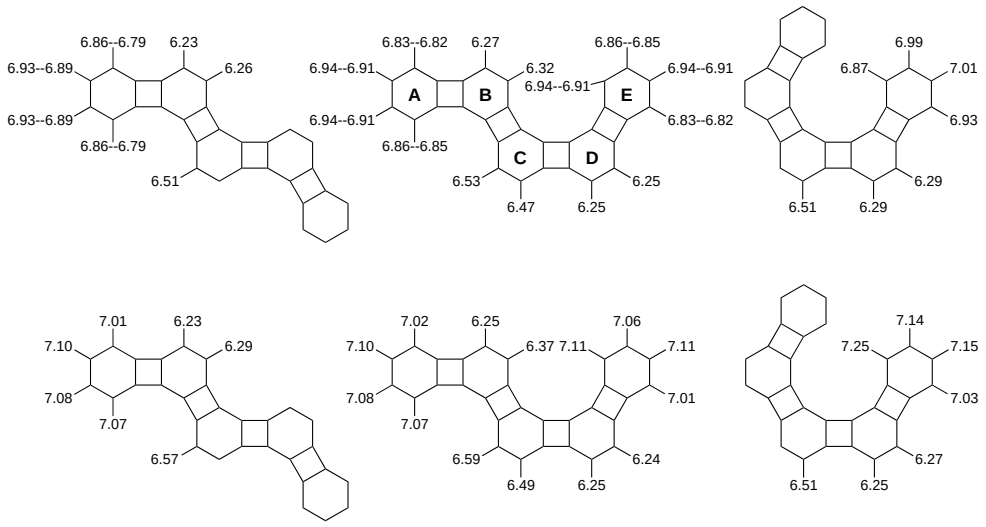


Figure 3.28: At the top: The actual proton chemical shifts of the zigzag-, anti zigzag- and angular-[5]-phenylene. At the bottom: The calculated values of the same compounds.

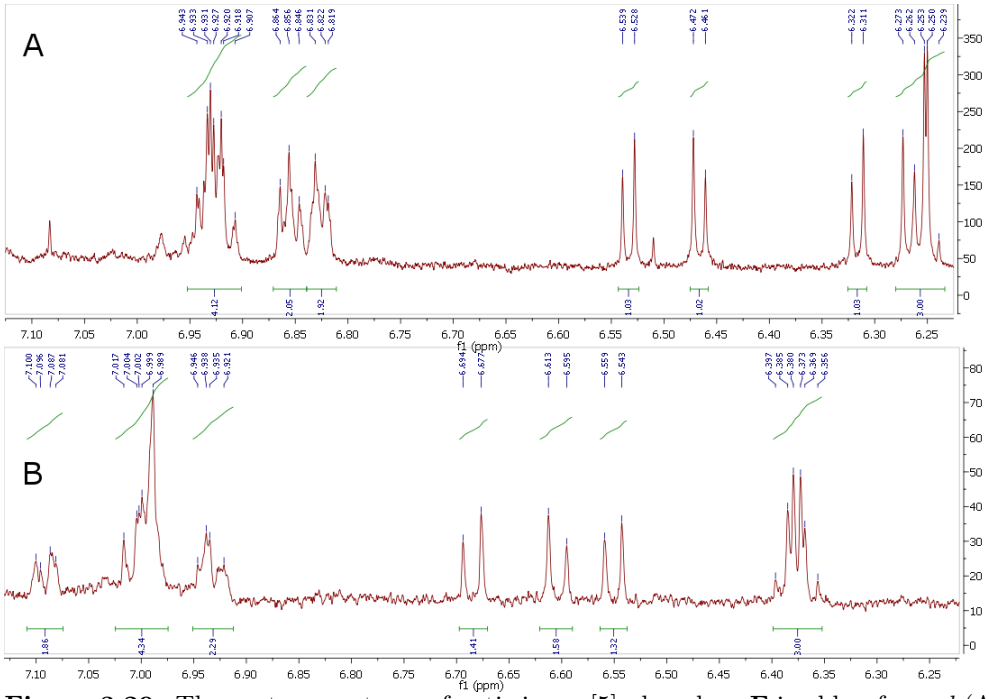


Figure 3.29: The proton spectrum of anti zigzag-[5]-phenylene **F** in chloroform-d (A) and acetone-d_6 (B).

chemical shifts of these two compounds, along with the calculated values for comparison,[78] are shown in figure 3.28.

Based on the spectra of these two similar compounds, as well as the calculated values, the following assignment has been made for the peaks of the proton NMR spectrum of anti zigzag-[5]-phenylene **F**, shown in figure 3.29. The top spectrum is recorded in deuterated chloroform, while the bottom one is recorded in deuterated acetone. The actual assignment is shown in figure 3.28, and gives the values from the spectrum recorded in $CDCl_3$.

Furthest upfield in the $CDCl_3$ spectrum is what seems at first glance to be a doublet at 6.25 ppm, integrating for two protons, but the coupling constant between these two peaks (1.7 Hz) is too small. Looking closer one may notice that there is a small shoulder peak at 6.239 (a similar shoulder peak would be found on the opposite side of the central "doublet", if it wasn't obscured by the doublet at 6.27). These peaks correspond to an AB system lying at only 1.7 Hz distance, with a coupling constant of 6.6 Hz. The pattern can be seen more easily from the bottom spectrum, when disregarding the two peaks at 6.385 and 6.369, which origin from the next doublet downfield. From the bottom spectrum the coupling constant is 6.8 Hz. This AB system corresponds to the

protons on ring D, as the signals from these would be expected to be at the highest field, very close to each other and each of them split into a doublet from the other one. The chemical shifts of 6.25 and 6.24 fit the calculated values of 6.25 perfectly, and the AB system at highest field is similar to the one observed for the zigzag- and angular-[5]-phenylene.

Moving downfield the next signals one encounter in the top spectrum are two doublets at 6.27 and 6.32, respectively, which couple to each other with a coupling constant of 6.6 Hz. These peaks are assigned to the protons on the B ring because these are expected to be found at almost as high field as the ones on the D ring, but with a lot larger distance between them. Again the chemical shifts fit the theoretical values of 6.25 and 6.37 very well.

Moving further downfield the next peaks are another set of doublets, at 6.47 and 6.53 ppm respectively. The doublets couple to each other with a coupling constant of 6.8 Hz. These peaks are assigned to the protons on the C ring, as the protons on the central ring are expected to be at a lower field than the protons on the B and D rings, but still upfield compared to the protons on the terminal rings. The chemical shifts fit the calculated values of 6.49 and 6.59 very well.

Furthest upfield is 3 multiplets at 6.83–6.82, 6.86–6.85 and 6.94–6.91 ppm, with an integral ratio of 2:2:4. These signals are assigned to the eight protons on the terminal rings, as these are expected to be the most aromatic and thus their signals expected to be found at lowest field. The assignment of the individual multiplets to certain protons are shown in figure 3.28, but are based solely on comparison to the calculated values.

3.4 Summary and conclusions

To summarize what has been achieved the desired target molecule, anti zigzag-[5]-phenylene, was synthesized in ten steps from the commercially available starting material 1,2-dibromobenzene in an overall yield of 0.5 %. Six of the ten steps had not been performed before and six new compounds have been isolated and characterized in the process.

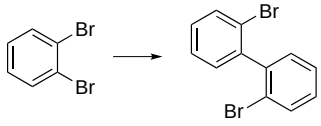
The target molecule was only characterized by HRMS and proton NMR, due to the unfortunate event that the compound decomposed while dissolved in deuterated chloroform. The experiments are ongoing in order to be able to obtain ^{13}C NMR and qualitative UV data as well as a single crystal x-ray diffraction structure.

3.5 Experimental part

All solvents used were bought from commercial suppliers, HPLC grade and distilled before use, using standard solvent purification methods. Reagents were bought from commercial suppliers and used without further purification unless otherwise is stated: NBS was recrystallized from water and $CpCo(CO)_2$ was vacuum transferred immediately prior to use. All reactions were performed under N_2 in ovendried glassware. Flash Column Chromatography was performed on silica gel (ICN SiliTech 32-63 D 60 Å).

Melting points were recorded in open capillary tubes on a Thomas Hoover Unimelt Capilary Melting Point Apparatus and are uncorrected. All NMR spectra were recorded on a Bruker 400 MHz or a Bruker 600 MHz apparatus; chemical shifts are reported in ppm from lowest to highest field, using or the solvent residual peak as internal standard. IR spectra was recorded on a PerkinElmer Spectrum100 FT-IR spectrometer and are reported in wavenumbers (cm^{-1}) in decreasing order. Mass Spectrometry was performed by the qb3 MS facility at UC Berkeley.

2,2'-Dibromobiphenyl



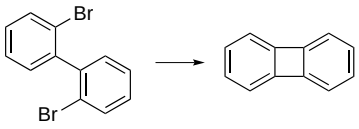
An ovendried 250 ml three-necked roundbottomed flask equipped with a stirring bar, two septa and a low temperature thermometer was cooled down to room temperature under a flow of N_2. 1,2-Dibromobenzene (12.095 g; 51 mmol) and dry THF (120 ml) was placed in the flask and the solution was cooled down in a dry ice/acetone bath. *n*-BuLi (1.6 M in hexane; 17.0 ml; 27.2 mmol) was added via syringe at such a rate that the temperature never rose above -70 °C. After addition the cooling bath was removed and the temperature allowed to reach 5 °C.

The reaction was hydrolyzed with 30 ml 5 % (v/v) HCl and the resulting phases were separated. The aqueous phase was extracted with diethyl ether (3 x 50 ml) and the combined organic phases were washed with water (2x30 ml), dried over anhydrous $MgSO_4$, filtered through a fluted filter paper and concentrated in vacuo. The residue was dissolved in the minimum amount of diethyl ether possible and absolute ethanol (15 ml) was added, whereby a solid precipitated. The solid was filtered off on a büchner funnel to yield 2,2'-

dibromobiphenyl as off-white crystals (3.4493 g; 11.1 mmol; 43 %), melting at 78–79 °C (lit. 80-81 °C[112]). The mother liquor was concentrated in vacuo, the residue dissolved in diethyl ether, absolute ethanol was added and the flask placed in a freezer over night, which caused more solid to precipitate. The liquid was removed with a pipette and the solid dried to yield 2,2'-dibromobiphenyl as pale orange crystals (1.99 g; 6.4 mmol; 25 %), melting at 74–75 °C.

^{1}H-NMR(400 MHz, $CDCl_3$) δ 7.67 (d, J = 7.7 Hz, 2H), 7.40–7.36 (m, 2H), 7.29–7.24 (m, 4H). ^{13}C-NMR(101 MHz, $CDCl_3$) δ 142.0, 132.6, 131.0, 129.4, 127.1, 123.5. The observed chemical shifts are in accordance with the literature values.[133]

Biphenylene



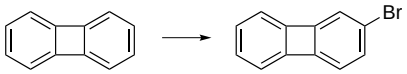
An ovendried 100 ml three-necked roundbottomed flask equipped with a stirring bar, two septa and a low temperature thermometer was cooled down to room temperature under a flow of N_2. 2,2'-dibromobiphenyl (0.636 g; 2 mmol) and dry THF (40 ml) was placed in the flask and the solution was cooled down in a dry ice/acetone bath. *n*-BuLi (1.6 M in hexane, 3.3 ml; 5.3 mmol) was added dropwise via syringe, at such a rate that the temperature did not rise above -72 °C. After the addition was complete the reaction was stirred for 2 hours at the lowest possible temperature, then the temperature was allowed to rise to -50 °C and $ZnCl_2$ (0.5 M in THF; 5 ml; 2.5 mmol) was added via syringe. After the addition was complete the reaction was stirred for 2 hours at -50 °C (± 2 °C), then the temperature was lowered to the minimum afforded by a dry ice/acetone bath and anhydrous cupper(II)chloride (0.869 g; 6.5 mmol) was added. The reaction was left in the cooling bath over night, allowing it to slowly reach room temperature.

The reaction was hydrolyzed with 5 % (v/v) HCl (10 ml) and the resulting phases separated. The aqueous phase was extracted with toluene (2x10 ml) and the combined organic phases were washed with water (2x10 ml). The combined aqueous phases were extracted again with toluene (10 ml) and the combined organic phases were washed with water (10 ml), dried over anhydrous $MgSO_4$, filtered through a fluted filter paper and concentrated in vacuo. The residue was dissolved in diethyl ether and filtered through a Celite plug in a glass filter funnel. The filtrate was concentrated in vacuo to yield the crude product as

an off-white solid. The crude product was dissolved in the minimum amount of diethyl ether and methanol was added dropwise until the solution began to look cloudy. The solution was placed in the freezer for several hours, whereby precipitation occured. The liquid was removed with a pipette, leaving the product as colorless needleshaped crystals (0.126 g; 0.8 mmol; 41 %), melting at 103.5-104.5 °C (lit. 111 °C[89]).

^{1}H-NMR(400 MHz, $CDCl_3$) δ 6.74–6.72 (m, 4H), 6.63–6.61 (m, 4H). ^{13}C-NMR(101 MHz, $CDCl_3$) δ 151.4, 128.2, 117.3. The observed chemical shifts are in accordance with the literature values.[94]

2-Bromobiphenylene

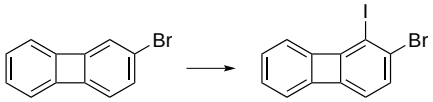


An ovendried 50 ml roundbottomed flask equipped with a septum and a magnetic stirring bar was cooled down to room temperature under N_2-flow. Biphenylene (0.5853 g; 3.85 mmol) and N-bromosuccinimide (0.6844 g; 3.85 mmol) was placed in the flask, DMF (14 ml) was added and the solution was stirred at room temperature overnight.

The solution was poured into a separatory funnel and water (50 ml) was added. The resulting dispension was extracted with diethyl ether (3 x 50 ml) and the combined organic phases were washed with water (3 x 25 ml), dried over $MgSO_4$, filtered through a fluted filter paper and concentrated in vacuo to yield the crude product as a yellow solid. The crude product was purified on a short silica column, eluting with petroleum ether, to yield the product as a pale yellow solid (0.6274 g; 2.7 mmol; 70 %).

^{1}H-NMR(400 MHz, $CDCl_3$) δ 6.90 (dd, J = 7.3, 1.5 Hz, 1H), 6.80–6.74 (m, 3H), 6.68–6.63 (m, 2H), 6.49 (d, J = 7.3 Hz, 1H). ^{13}C-NMR(101 MHz, $CDCl_3$) δ 152.7, 150.2, 149.9, 149.7, 130.5, 129.0, 128.5, 121.5, 121.1, 118.6, 118.0, 117.8. The observed proton chemical shifts are in accordance with the chemical shifts reported in the research reports of former members of the Vollhardt group Dr. Florian Montermini and Dr. Alex Ho-Fai Lee. No published reference exists, to the best of our knowledge, to which the carbon chemical shifts could be compared.

2-Bromo-1-iodobiphenylene

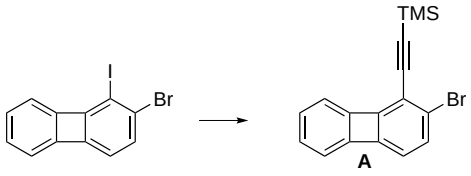


An ovendried 50 ml two-necked roundbottomed flask equipped with two septa and a stirring bar was cooled down to room temperature under N_2-flow. The product from the previous reaction (0.2321 g corresponding to 0.19 g; 0.8 mmol 2-bromobiphenylene) was placed in the flask and dissolved in dry THF (20 ml). The solution was cooled down in a dry ice/acetone bath and lithium diisopropyl amide (2M in THF/heptanes/ethylbenzene; 2 ml; 4 mmol) was added via syringe over a period of 20 minutes. The reaction was stirred for 2 hours in the cooling bath, then solid iodine (0.712 g; 2.8 mmol) was added. Reaction was left stirring under N_2 over night, allowing it to slowly reach room temperature.

The reaction was quenched with $Na_2S_2O_3$ (aq.) and extracted with diethyl ether (2 x 50 ml). The combined organic phases were washed with water (2 x 15 ml), dried over anhydrous Na_2SO_4, filtered through a fluted filter and concentrated in vacuo. The residue was purified by flash chromatography (eluting with hexane:DCM 15:1) to give a pale yellow solid (0.19 g; 0.5 mmol; 65 %).

^{1}H-NMR(400 MHz, $CDCl_3$) δ 7.01 (d, J = 7.1 Hz, 1H), 6.86–6.80 (m, 3H), 6.69–6.64 (m, 1H), 6.42 (d, J = 7.2 Hz, 1H). ^{13}C-NMR(101 MHz, $CDCl_3$) δ 158.9, 150.8, 150.9, 148.4, 131.5, 129.8, 128.6, 127.5, 118.0, 117.8, 116.6, 87.8. The observed chemical shifts are in accordance with the literature values.[115]

Compound A



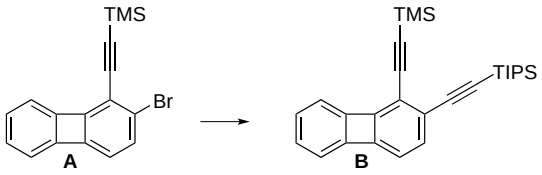
In an ovendried Schlenk-flask equipped with a condenser and a magnetic stirbar was placed the product from the previous reaction (0.234 g corresponding to at most 0.1687 g; 0.47 mmol of 2-bromo-1-iodobiphenylene), $PdCl_2(PPh_3)_2$ (23.4 mg; 0.033 mmol; 5 mol %) and CuI (9.9 mg; 0.052 mmol; 7.9 mol %).

The flask was evacuated and purged with N_2 several times and Et_3N (4 ml) was added via syringe. The flask was evacuated and purged with N_2 several times again and TMSA (0.2101 g; 2.1 mmol; 3.2 eq.) was added via syringe. The reaction was heated to 28 °C and stirred at this temperature under N_2 for two days.

The volatiles were removed in vacuo and the residue dissolved in petroleum ether. The dispension was filtered through a Celite plug in a glass filter funnel and the filtrate washed with water, dried over anhydrous $MgSO_4$, filtered through a fluted filter paper and concentrated in vacuo. The residue was purified by flash chromatography (eluting with petroleum ether) to yield the product as a yellow oil (97 mg; 0.30 mmol; 63 %).

^{1}H-NMR(400 MHz, $CDCl_3$) δ 6.98 (d, J = 7.3 Hz, 1H), 6.85–6.77 (m, 2H), 6.77–6.71 (m, 1H), 6.69–6.61 (m, 1H), 6.40 (d, J = 7.3 Hz, 1H), 0.28 (s, 9H); ^{13}C-NMR(101 MHz, $CDCl_3$) δ 155.1, 149.62, 149.58, 149.4, 131.4, 129.5, 128.8, 123.2, 118.4, 118.0, 118.0, 115.3, 102.3, 99.3, -0.15; IR (film) $\tilde{\nu}$ 3065 (vw), 2959 (w), 2161 (w), 1399 (m), 1248 (s), 1164 (m), 1157 (m), 839 (vs), 736 (vs) cm^{-1}; MS m/z (relative intensity) 326/327/328/329 (M^+, 40/10/41/10/3), 311/312/313/314 (28/7/29/7), 210/211 (65/12), 189 (20), 157 (12), 119 (20), 105/106 (100/59), 91/92 (81/68), 79 (17), 77 (22), 65 (12); HRMS calcd. for $C_{17}H_{15}BrSi$: 326.0126, found: 326.0128.

Compound B

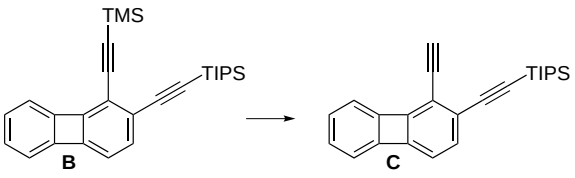


Compound **A** (0.0231 g; 0.07 mmol) was transferred to an ovendried Schlenk-flask by dissolving it in a few ml of petroleum ether. The volatiles were removed in vacuo. The Schlenk flask was equipped with a condenser and a magnetic stirbar, and $PdCl_2(PPh_3)_2$ (3.6 mg; 0.00525 mmol; 7.5 mol %) and CuI (3.0 mg; 0.0158 mmol; 22.5 mol %) was placed in the flask. The flask was evacuated and purged with N_2 several times and piperidine (2.5 ml) was added via syringe. The flask was again evacuated and purged with N_2 several times before TIPSA (50 μl; 0.0407 g; 0.22 mmol) was added via syringe and the reaction heated to 50 °C. The reaction was stirred at this temperature over night.

The volatiles were removed in vacuo, the residue dissolved in petroleum ether and the resulting dispension filtered through a Celite plug on a glass filter funnel. The filtrate was washed with water (2 x 10 ml), dried over $MgSO_4$, filtered through a fluted filter paper and concentrated in vacuo. The crude product was purified by flash chromatography (eluting with petroleum ether) to yield the product as a bright yellow oil (19.3 mg; 0.045 mmol; 64 %).

^{1}H-NMR(400 MHz, $CDCl_3$) δ 6.94 (d, J = 7.1 Hz, 1 H), 6.84–6.75 (m, 2 H), 6.72 (dd, J = 4.6, 2.4 Hz, 1 H), 6.64 (dd, J = 4.5, 2.1 Hz, 1H), 6.50 (d, J = 7.1 Hz, 1 H), 1.13 (s, 21H), 0.24 (s, 9H); ^{13}C-NMR(101 MHz, $CDCl_3$) δ 154.3, 150.6, 149.9, 149.8, 133.8, 129.3, 129.0, 124.2, 118.1, 118.0, 116.6, 114.5, 105.4, 100.8, 99.6, 94.1, 18.8, 11.3, -0.10; IR (film) $\tilde{\nu}$ 2943 (m), 2865 (m), 2154 (w), 1462 (m), 1415 (m), 1249 (m), 996 (w), 841 (s), 737 (s) cm^{-1}; MS m/z (relative intensity) 428/429/430/431 (M^+, 92/40/16/5), 385/386 (17/8), 343/344/345/346 (100/38/15/3), 315/316 (27/12), 301/302/303 (67/21/10), 269 (18), 241 (21), 210 (27), 158 (19), 105/106 (45/19), 91/92 (30/24), 73 (71), 59 (29); HRMS calcd. for $C_{28}H_{36}Si_2$: 428.2356, found: 428.2360.

Compound C

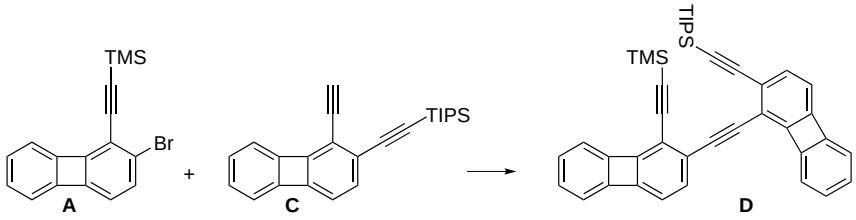


In a 10 ml roundbottomed flask was placed compound **B** (32.2 mg; 0.075 mmol), diethyl ether (2.5 ml), methanol (0.4 ml) and K_2CO_3 (20 mg; 0.15 mmol) under N_2. The reaction was stirred at room temperature over night. The solution was poured into a separatory funnel and water (10 ml) and diethyl ether (20 ml) were added. The phases were separated and the organic phase was dried over anhydrous $MgSO_4$, filtered through a fluted paper filter and concentrated in vacuo. The residue was purified by flash column chromatography (eluting with hexane:DCM 10:1) to yield the product as a yellow oil (26.1 mg; 0.073 mmol; 98 %).

^{1}H-NMR(400 MHz, $CDCl_3$) δ 6.96 (d, J = 7.1 Hz, 1 H), 6.82–6.79 (m, 2 H), 6.69–6.64 (m, 1 H), 6.53 (d, J = 7.1 Hz, 1 H), 3.27 (s, 1H), 1.13 (s, 21H); ^{13}C-NMR(101 MHz, $CDCl_3$) δ 154.0, 150.6, 149.9, 149.6, 133.5, 129.4, 129.1, 125.0, 118.4, 118.1, 116.8, 113.5, 105.1, 94.6, 83.0, 78.6, 18.7, 11.3; IR (film) $\tilde{\nu}$ 3303 (m), 3065 (w), 3027 (w), 2942 (m), 2863 (m), 2153 (m), 1461 (m), 1415

(m), 1402 (m), 1256 (m), 1157 (m), 996 (m), 920 (w), 875 (s), 826 (s), 743 (s), 709 (s), 677 (s), 656 (s) cm^{-1}; MS m/z (relative intensity) 356/357/358/359 (M^+, 75/35/11/2), 313/314/315/316 (100/42/14/2), 285/286 (39/15), 271/272 (58/25), 257 (39), 243 (65), 227/228/229 (43/39/30), 129 (76), 122 (38), 105 (20), 59 (20); HRMS calcd. for $C_{25}H_{28}Si$: 356.1960, found: 356.1964.

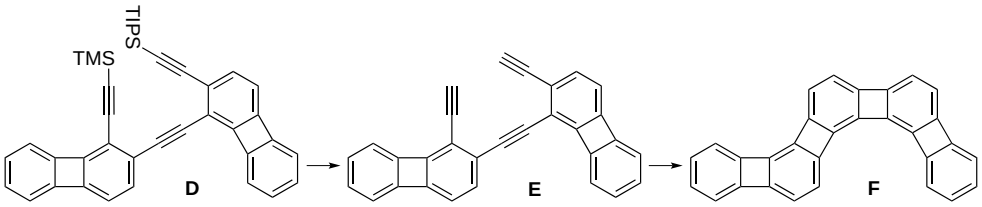
Compound D



In a 10 ml Schlenk bomb was placed compound **A** (18.5 mg; 0.056 mmol), $PdCl_2(PPh_3)_2$ (3.3 mg; 0.0047 mmol; 9.8 mol %) and CuI (1.3 mg; 0.0068 mmol; 14.2 mol %). The bomb was transferred to a glovebox and Et_3N (1.5 ml) and compound **C** (17 mg; 0.048 mmol) dissolved in THF (3.5 ml) was added. The bomb was sealed tightly and transferred to a fumehood where it was heated to 95-97 °C for two days. The volatiles were removed in vacuo. The residue was dissolved in DCM and filtered through a Celite plug on a glass filter funnel. The filtrate was washed with water (2 x 10 ml), dried over $MgSO_4$, filtered through a fluted filter paper and concentrated in vacuo. The residue was purified by flash chromatography (eluting with hexane:DCM, 50:1) to yield the product as an orange-red solid (9 mg; 0.0149 mmol; 31 %).

^{1}H-NMR(400 MHz, $CDCl_3$) δ 7.00–6.93 (m, 3 H), 6.84–6.77 (m, 5 H), 6.68–6.65 (m, 2 H), 6.55–6.51 (m, 2 H), 1.11 (s, 21H), 0.20 (s, 9 H); ^{13}C-NMR(101 MHz, $CDCl_3$) δ 154.1, 153.4, 150.9, 150.7, 149.94, 149.93, 149.89, 149.85, 133.8, 133.5, 129.3, 129.2, 129.1, 129.0, 124.4, 124.1, 118.6, 118.3, 118.0, 117.9, 116.5, 116.4, 114.6, 114.3, 105.6, 101.2, 99.8, 94.2, 94.0, 87.8, 18.7, 11.4, -0.01; IR (film) $\tilde{\nu}$ 3067 (vw), 2924 (m), 2863 (m), 2152 (w), 1463 (m), 1416 (m), 1375 (w), 1250 (m), 1157 (m), 1028 (m), 843 (s), 828 (s), 739 (s), 710 (m), 675 (m) cm^{-1}; MS m/z (relative intensity) 602/603/604/605 (M^+, 55/30/12/4), 559/560/561 (28/17/7), 530 (3), 517 (5), 502 (12), 486 (3), 475 (6), 443 (12), 415/416/417 (85/32/11), 401 (9), 249-235-221-207-193-179-165-151 (<8), 137 (8), 129 (31), 125 (13), 111 (22), 97 (33), 87 (29), 85 (22), 83 (31), 81 (18), 73 (100), 71 (33), 69 (31), 59 (36), 57 (52); HRMS calcd. for $C_42H_42Si_2$: 602.2825, found: 602.2831.

Anti Zigzag-[5]-phenylene F



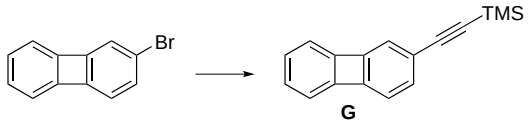
In a 10 ml roundbottomed flask equipped with a magnetic stirbar and a septum was placed compound **D** (9 mg; 0.0149 mmol) and dry THF (5 ml). The solution was degassed with N_2 until 3 ml was left. Ethanol (10 μl) and TBAF (1.0 M in THF; 100 μl; 0.1 mmol; 3 eq.) was added and the solution was stirred under N_2 at room temperature for one hour. By TLC (hexane:DCM 10:1) no starting material was present. The solution was poured into a separatory funnel containing diethyl ether (10 ml) and water (8 ml) under N_2. The phases were separated after vigorous shaking and the organic phase was dried over $MgSO_4$, filtered through a fluted paper filter and concentrated in vacuo to yield compound **E** as a yellow slurry. The flask was transferred immediately to a Schlenk line and evacuated and purged with N_2 several times.

A 25 ml Schlenk flask equipped with a condenser, a septum and a magnetic stirbar was evacuated and purged with N_2 several times. Dry toluene (5 ml) was placed in the flask and brought to reflux while under irradiation by a 300 W halogen lamp. Compound **E** and $CpCo(CO)_2$ (10 μl; 13.5 mg; 0.075 mmol) was dissolved in dry toluene (10 ml) and added via a syringe through the septum at the top of the condenser at a rate of approximately 5 ml/h, using a syringe pump. After the addition was complete the condenser was washed down with a few ml of dry toluene and the reaction was refluxed under irradiation for an additional 30 minutes. The flask was cooled down, purged with N_2 and stored at -75 °C over night. The volatiles were removed in vacuo and the residue purified by flash chromatography (eluting with hexane:DCM, 10:1; R_f 0.62) to yield the product as a yellow solid (3.9 mg; 1:1.3 mixture of product and dioctyl phthalate; 0.0044 mmol; 30 %).

^{1}H-NMR(600 MHz, $CDCl_3$) δ 6.94–6.91 (m, 4H), 6.86–6.85 (m, 2H), 6.83–6.82 (m, 2H), 6.53 (d, J = 6.8 Hz, 1H), 6.47 (d, J = 6.8 Hz, 1H), 6.32 (d, J = 6.6 Hz, 1H), 6.27 (d, J = 6.6 Hz, 1H), 6.25 (AB, J = 6.6 Hz, 2H). ^{1}H-NMR(400 MHz, Acetone-d_6) δ 7.12–7.07 (m, 2H), 7.03–6.97 (m, 4H), 6.96–6.91 (m, 2H), 6.69 (d, J = 6.9 Hz, 1H), 6.60 (d, J = 6.9 Hz, 1H), 6.55 (d, J = 6.5 Hz, 1H), 6.38 (d, J = 6.5 Hz, 1H), 6.38 (AB, J = 6.8 Hz, 2H). MS m/z (relative intensity) 374/375/376 (M^+, 15/5/1), 217 (2), 177/178 (19/6), 148/149 (51/7), 137/138

(27/3), 121 (69), 120 (51), 92 (28), 86 (72), 84 (100), 65 (12), 57 (11), 51 (43); HRMS calcd. for $C_{30}H_{14}$: 374.1096, found: 374.1097.

Compound G



G

Reacting a mixture of 2-bromobiphenylene, 2,6-dibromobiphenylene and 2-bromo-1-iodobiphenylene by the same synthetic procedure as for the preparation of compound **A**, only raising the temperature to 35 °C, resulted in the formation of compounds **G**, **H** and **I**, which could be separated by flash chromatography, eluting with PE, to yield compound **G** as a pure product and compounds **H** and **I** as an inseparable mixture.

Compound G: ^{1}H-NMR(400 MHz, $CDCl_3$) δ 6.92 (dd, J = 7.1, 1.1 Hz, 1H), 6.77 (dd, J = 4.9, 2.9 Hz, 2H), 6.71–6.62 (m, 3H), 6.57 (dd, J = 7.1, 0.7 Hz, 1H), 0.23 (s, 9H); ^{13}C-NMR(101 MHz, $CDCl_3$) δ 151.3, 150.8, 150.5, 150.4, 132.9, 128.7, 128.6, 122.5, 119.8, 117.8, 117.8, 116.9, 105.7, 93.9, -0.06. MS m/z (relative intensity) 328 (M^+, 6), 313 (3), 248/249/250 (85/31/11), 233/243/235 (100/36/13), 217 (15), 203 (18), 189 (17), 117 (35), 102 (10); HRMS calcd. for $C_{17}H_{16}Si$: 248.1021, found: 248.1020.

CHAPTER 4

Manganese catalyzed radical formation of styryl derivatives

This chapter describes the serendipitous discovery of a new method for the formation of styryl derivatives by a radical reaction of THF and other cyclic ethers with β-bromostyrenes. The optimized reaction conditions involve addition of three to four equivalents of Me_2Zn to a solution of β-bromostyrene, using the radical precursor as solvent, in the presence of 10–12 % of $MnCl_2$, and subsequently refluxing overnight. A simple aqueous workup and purification by column chromatography yields the products in moderate to good yields. The radical precursor can be a cyclic or an acyclic ether or even a cycloalkane, although the latter gives only poor yields. The β-bromostyrene can be substituted with electron donating or electron withdrawing substituents without affecting the yield of the reaction remarkably. A preliminary mechanistic investigation indicates a radical non-chain mechanism, but the details of the mechanism are unknown.

4.1 Introduction

The palladium catalyzed cross coupling reactions are among the most widely utilized catalytic reactions in organic chemistry. Palladium is an efficient catalyst, but suffers from the drawbacks of being both expensive and toxic and therefore the pursuit of new catalytic systems to perform similar reactions is ever ongoing. A broad range of different transition metals have been explored in this regard, but manganese seems for the most part to have been overlooked,

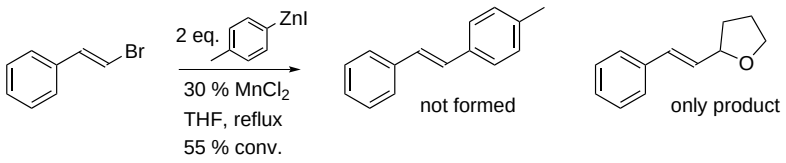


Figure 4.1: The reaction of β-bromostyrene and *p*-tolylzinc iodide in THF results in the formation of (*E*)-2-styryltetrahydrofuran and not the anticipated Negishi coupling product 1-methyl-4-styrylbenzene.

despite the fact that it is both cheap, abundant and of negligible toxicity. In short these were the motivations which lead to a preliminary study of the use of manganese salts as precatalysts in cross coupling reactions, described in detail in section 4.2.

In an attempt to perform a manganese catalyzed Negishi coupling β-bromostyrene was reacted with two equivalents of *p*-tolylzinc iodide in the presence of 30 % of $MnCl_2$ in refluxing THF. Surprisingly the product from the reaction proved not to be the anticipated Negishi coupling product 1-methyl-4-styrylbenzene, but 2-styryltetrahydrofuran from the reaction of β-bromostyrene with the solvent. The reaction is shown in figure 4.1.

Since some zinc compounds can act as radical initiators and THF is known to form radicals readily in the 2-position, the observed product was believed to be formed by the addition of a tetrahydrofuranyl radical to β-bromostyrene followed by elimination of a bromoradical. The reaction seemed to be stereoselective as only the E-enantiomer was detected, no byproducts were observed and the conversion of the starting material was around 55 %. The reaction does run in the absence of $MnCl_2$ but the yields are greatly improved when it is present. The reaction had not previously been reported in the literature and therefore a further investigation of the reaction and its possibilities was initiated, leading ultimately to the development of a new method for the formation of a variety of styryl derivatives.

4.1.1 The basics of radical chemistry

Radicals are atoms or molecules which contain one or more unpaired electrons, usually rendering them unstable and therefore highly reactive. Lavoisier is credited for being the first to use the term 'radical' in a chemical context in 1789, but in an entirely different meaning than in modern chemistry, as he used the word to describe the part of an acid which is not oxygen.[134] Later on the word was used to describe substituents like the methyl- and ethyl- groups, and only during the latter part of the 19th century did the term become associated with species of an extraordinarily high reactivity. The first organic free radical

to be identified as such was the triphenylmethyl radical, which was discovered by Gomberg in 1900.[135] In the decades that followed more reactive radicals were discovered, leading to the development of different polymers by the radical chain-reaction of alkenes. Up until the 1970s this was more or less the only use for radical chemistry, as the reactivity of the radicals seemed impossible to control for the synthesis of small molecules. This changed with the study of radical reaction rates and the appearance of advanced analytical methods like ESR, which made it possible to detect short-lived radical intermediates. The enhanced understanding of the radical reaction mechanism that this information provided made it possible to design radical reactions suited for the synthesis of small organic molecules, and the field of radical chemistry has been in rapid growth ever since.[134]

Radicals can be formed in a number of ways: By homolytic cleavage, by single electron transfer or by reaction with another radical. By homolytic cleavage a weak covalent bond is broken by applying either heat, light, radiation or ultrasound, known as thermolysis, photolysis, radiolysis and sonolysis, respectively. The electronpair constituting that bond is split and one electron goes to each of the two halves of the molecule, forming two radical species in the process. By single electron transfer a radical is formed by either addition or loss of a single electron to or from a neutral molecule. Addition of one electron is a reduction, resulting in the formation of a radical anion, whereas loss of one electron is an oxidation, forming a radical cation. The reductant or oxidant can be either an electrode or a molecule, the latter usually being a metal salt where the change of the oxidation state by one comes easily. Finally the reaction between a radical and a non-radical species results in the formation of a new radical by either abstraction or addition.[134]

A radical reaction in general can be thought of as consisting of three distinct steps: Initiation, propagation and termination. The steps are shown schematically in figure 4.2. In the initiation step a radical species is formed, either by homolysis or single electron transfer as described above. The radical is formed

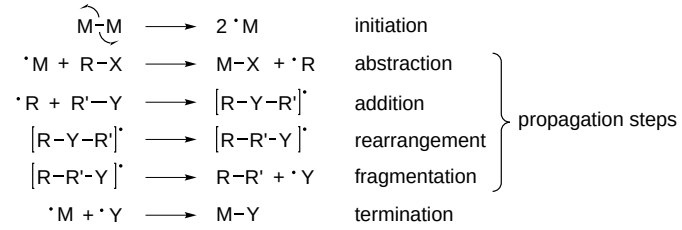


Figure 4.2: A schematic representation of the three different overall steps of a radical reaction: Initiation, propagation and termination. The propagation can consist of some or all of the shown steps.

in either catalytic or stoichiometric amounts depending on whether the reaction is a chain or a non-chain reaction. The initially formed radical species then reacts with another molecule, setting off a sequence of reactions known as the propagation steps, also outlined in figure 4.2. These steps would typically commence with the abstraction of an atom or group, most often a hydrogen or halogen, from another molecule, thereby forming a new radical species. This new radical will then react further by one or more of the different propagation steps available (abstraction, addition, rearrangement, fragmentation) before it finally terminates. The termination step can happen in three different ways: Two radicals can combine to form a non-radical species (combination), a radical can lose an electron to form a cation (oxidation) or it can receive an electron forming an anion (reduction).[134]

Carbon centered radicals $R_3C^{\bullet}$ can be either planar or pyramidal in shape, depending on whether the unpaired electron occupies a p-orbital or an sp^3 hybrid. The observed shape is highly dependent on the size and electronic density of the R-groups: The more sterically demanding the R-group, the higher the tendency to form planar radicals, in order to minimize the steric interactions of the substituents.

Although all radicals in principle can be considered unstable and thus highly reactive, this is obviously a gradient spanning a broad spectrum. It is important to differentiate between the ease of formation, which is mainly controlled by how easily the bond is homolyzed, and the thermodynamic stability of the formed radical species. Once a radical is formed, some will be extremely reactive and thus have a very short lifetime, whereas others, due to stabilization by for example resonance, will have a much longer lifetime. The more stable the formed radical is, the more selective it will be in terms of what it reacts with, and that in turn renders it more useful for controlled synthesis of small organic molecules.[134]

Thus a radical reaction can be designed when combining knowledge of the stability and reactivity of the radical species with the different steps that the reaction must undergo. Firstly, the initiator must contain one or more bonds which are easily broken, whereby the initial radical species can be formed under as mild conditions as possible. Some of the most widely used radical initiators include organometallic compounds with a metal-metal bond, azocompounds and peroxides. Common for all three groups of compounds are that they contain a rather weak single metal-metal, heteroatom-heteroatom or carbon-heteroatom bond, which can be easily cleaved by thermolysis or photolysis.[134]

The factors governing the abstraction of radical atoms or groups from neutral molecules are a combination of the ease with which the bond is broken and the stability of the resulting radical. Thus a halogen atom is easily abstracted because a C-X bond is fairly weak, whereas a hydrogen α to a heteroatom or

a phenyl group is easily abstracted due to the resonance stabilization available to the resulting radical.[134]

4.1.2 Formation and reactions of α-tetrahydrofuranyl radicals

The formation of α-alkoxy radicals by the action of a radical initiator is well known. THF in particular has been used as a radical precursor, forming the α-tetrahydrofuranyl radical with a wide array of radical initiators, including Bz_2O_2, DTBP, Et_3B and Me_2Zn just to mention a few which will be described in further detail in this section. The α-tetrahydrofuranyl radicals are nucleophilic and several examples exist where these radicals have been added to C=C, C=O and C=N double bonds as well as C≡C triple bonds. In contrast hereto only a single example of an addition-elimination reactions exists. A representative range of reactions are presented in the current section and shown in figure 4.3.

In 1990 McCarthy and coworkers reported the addition of α-alkoxy radicals to 1-fluoro-1-(phenylsulfunyl)-ethylene in good to moderate yields. The radicals were formed from THF, 2-methyltetrahydrofuran, 1,3-dioxolane, 1,4-dioxane and propanal by employing either catalytic amounts of benzoyl peroxide or zinc dust.[136] Same year Lukevics and coworkers reported the addition of THF and tetrahydrofuranone radicals to alkenylsilanes in the presence of di-*t*-butylperoxide.[137] Tu and coworkers reported the use of $TiCl_4$ and a rhodium catalyst for the coupling of THF and alkenes by C-H activation of the ether. The radical intermediate is trapped with chloride radicals, resulting in the final products being α-chloro-β-THF-alkyls.[138]

Yoshimitsu and Nagaoka reported in 1999 the addition of THF radicals to aldehydes forming α-substituted tetrahydrofuran-2-methanols. The THF radicals were formed by using three equivalents of Et_3B in THF and the reaction gave only moderate yields.[139] Subsequently the yields were improved significantly by using a mixture of 10 equivalents of Et_3B and 6 equivalents of *t*-butyl hydroxyperoxide.[140]

In 2002 Tomioka and coworkers reported the incidental discovery of the formation of THF radicals by Me_2Zn and air.[141] In an attempt to add a methyl group to an imine with Me_2Zn in THF as solvent they obtained addition of THF to the imine in 95 % yield instead. The reaction was performed under argon, but when great care was taken to avoid any air present the yield dropped to only 4 %, whereas the reaction rate was greatly enhanced by a constant flow of air through the solution, strongly indicating that a radical mechanism is in play. Most likely the reaction is initiated by the formation of a methyl radical from the S_H2 reaction of Me_2Zn with oxygen, which is the case for similar reactions with diethylzinc and triethylborane.[142] The reaction is quite general with ethers, and 1,3-dioxolane, THP, 1,4-dioxane and Et_2O were added

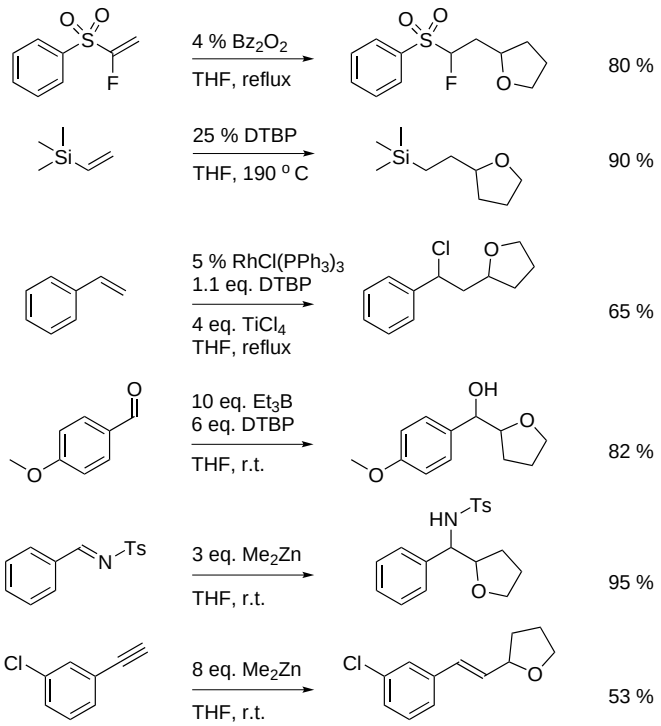


Figure 4.3: A representative range of reaction conditions and yields for the addition of α-tetrahydrofuranyl radicals to double bonds. From top to bottom: McCarthy 1990,[136] Lukevics 1990,[137] Tu 2008,[138] Yoshimitsu and Nagaoka 2002,[140] Tomioka 2002,[141] Chen and Guo 2009.[144]

to the imine in good yields. Attempts were made to perform the reaction using other radical initiators: With benzoyl peroxide no reaction occured, and with triethyl borane and air only the ethyl-adduct was observed. Diethyl zinc and diisopropyl zinc resulted in the ethyl– and isopropyl adduct as well as reduction of the imine. The authors hypothesize that the difference in reactivity is due to the low stability of the methyl radical compared to the ethyl- or isopropyl radical, causing it to react immediately with the solvent which is in great excess.

In a subsequent study the authors report that they obtain differentiation between addition of the THF-radical to either an imine or an aldehyde, depending on whether Me_2Zn or Et_3B was used as radical initiator.[143] This finding may indicate that the role of the radical initiator expands beyond mere initiation and also involves activation of the substrate somehow, but the authors provide no explanation for their observations.

Chen and Guo reported the radical addition of THF to electron deficient phenylacetylenes (figure 4.4), initiated by either Me_2Zn or Et_3B.[144] The reac-

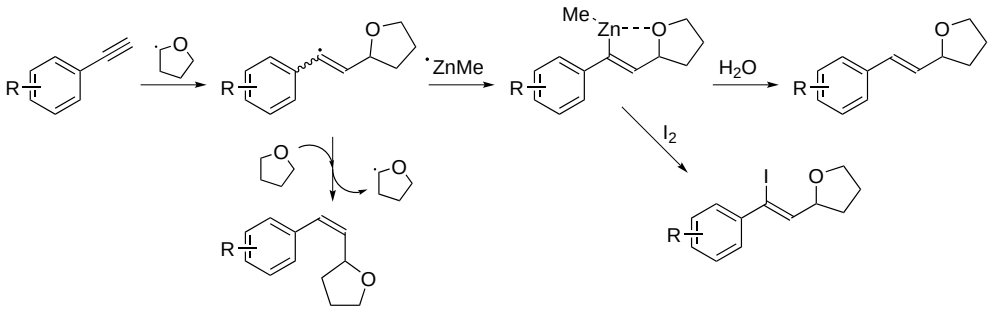


Figure 4.4: Use of Me_2Zn as radical initiator results mainly in the formation of the E-isomer, possibly due to the formation of a 5-membered zincacycle intermediate. Evidence for the occurence of this organozinc intermediate is given by the formation of an α-iodo species when quenching the reaction with iodine.

tion proceed with high E-selectivity when employing Me_2Zn as radical initiator, whereas the Z geometry was preferred when employing Et_3B. The difference in selectivity is explained by the possible trapping of the intermediate vinylic radical by a zinc species when using Me_2Zn as initiator. The zinc atom supposedly coordinates to the oxygen atom of THF in a 5-membered metallacycle, thus stabilizing the E-geometry. The organozinc intermediate performs a zinc-proton exchange under aqueous workup or decomposes upon reaction with air. The existence of the organozinc compound is substantiated by the fact that quenching the reaction with iodine results in formation of the α-iodo compound, presumably by a zinc-iodine exchange mechanism. The mechanism is shown in figure 4.4.

The small amount of Z-isomer observed is envisioned to arise by abstraction of a hydrogen from the solvent by the vinylic radical intermediate. This theory is supported by the fact that upon quenching the reaction with D_2O a large amount of deuterium incorporation in the α-position is observed for the E-isomer but almost none in the Z-isomer. In the case where Et_3B is used as radical initiator this stabilization of the E-vinylic intermediate is not possible, and formation of the Z-isomer is preferred for steric reasons.

To the best of our knowledge the only example of an addition-elimination reaction similar to the one we report was presented by Yao and coworkers in 2003. They reported the formation of different styryl derivatives by the addition-elimination reaction of THF and cycloalkyl radicals with β-nitrostyrenes.[145] The reaction is shown in figure 4.5. The group had previously reported the formation of alkenes from a similar reaction of β-nitrostyrenes with alkyl radicals from trialkylboranes[146] and with alkyl radicals from the reaction of alkyl iodides with Et_3B.[147] By using benzoyl peroxide as radical initiator instead of Et_3B they now observed formation of THF radicals when using THF as solvent,

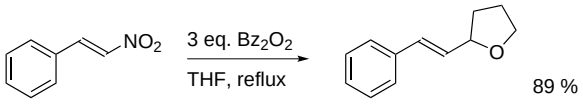


Figure 4.5: The addition-elimination reaction of the α-tetrahydrofuranyl radical with β-nitrostyrene presented by Yao and coworkers.[145]

leading to 2-styryltetrahdrofuran. The reaction proved to be quite general and could also be used with THP and 1,3-dioxolane as solvent, as well as a selection of cycloalkanes ranging from five to eight carbons. Later they also reported the reaction of β-nitrostyrenes with aldehyde radicals.[148]

4.1.3 Manganese in radical chemistry

Manganese is not an unknown player in the field of radical chemistry. Mn(0) can be used as radical initiator in the combination with organohalides[149] and the Mn(III) compound $Mn(OAc)_3$ is widely used as an efficient one electron oxidant.[150] Furthermore several examples exist where Mn(II) species are either oxidized or reduced to give catalytically active species for radical reactions.[151] The current section will provide a brief overview of the use of different low-valent manganese compounds as initiators, catalysts or reagents in radical reactions.

When employing a transition metal as catalyst in a reaction it can sometimes be difficult to determine whether the reaction occurs by regular transition metal catalysis or by a radical mechanism. The mechanism in a regular transition metal catalyzed reaction usually commences with an oxidative addition, which is a two-electron transfer from the metal center to the substrate, forming a new organometallic species and increasing the formal oxidation state of the metal center by two. This step is followed at some point by a reductive elimination, which is the opposite two-electron transfer reaction regenerating the original catalyst. For a radical reaction the mechanism is instead a single electron transfer (SET). Which of the two pathways is followed is determined by the nature of the metal, the ligands and the substrates involved in the reaction. Sometimes the two types of mechanisms even overlap or combine.[151]

The ease by which a metal complex performs a SET can be roughly estimated by looking at the first ionization energy of the complex. The lower the energy, the easier it is for the complex to loose an electron by transferring it to a substrate. The 3d metals have a lower first ionization energy than their 4d and 5d counterparts, and the same goes for low-valent metal complexes compared to those of a higher valence. Thus, the SET pathway is most commonly observed with low valent complexes of the first row transition metals.[151] Manganese 0, 1, 2 and 3 fit well into this category.

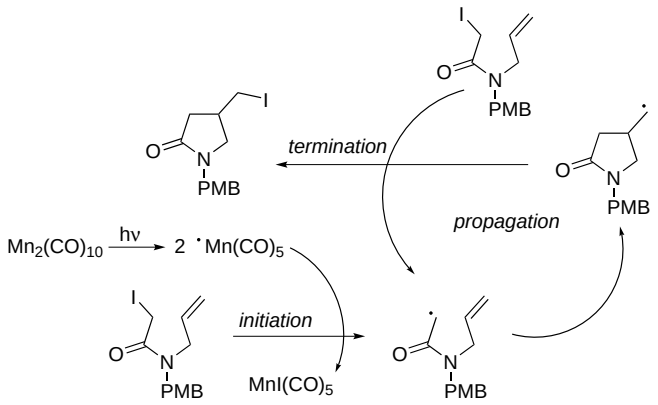


Figure 4.6: The radical cyclization of *N*-allyl iodoacetamide initiated by $Mn_2(CO)_{10}$ reported by Parsons and coworkers.

Manganese(0) The only commercially available manganese(0) complex is $Mn_2(CO)_{10}$. The Mn–Mn bond is rather weak, with bond energies varying from 142 to 159 kJ mol^{-1} depending on how it is calculated, and thus is easily cleaved, either photolytically, thermally or chemically.[152] Photolysis can result in the formation of two different species: The 17e$^-$ radical $^{\bullet}Mn(CO)_5$ and the complex $Mn_2(CO)_9$ from the dissociation of a ligand.[153]

Parsons and coworkers reported the use of catalytic amounts of $^{\bullet}Mn(CO)_5$ from photolysis of $Mn_2(CO)_{10}$ as initiator for the radical formation of 5-membered rings.[154] The Mn radical abstracts iodine from a *N*-allyl iodoacetamide and the resulting C radical cyclizes intramolecularly to form a 4-methylpyrrolidinone radical which subsequently terminates by abstraction of an iodine from the starting material, thus continuing the catalytic cycle (figure 4.6). Friestad utilized the affinity for halogen abstraction which is inherent to the pentacarbonyl manganese radical to perform stereoselective addition of alkyl radicals from alkyl iodides to *N*-acylhydrazones, forming chiral hydrazines with oxazolidinone auxiliaries attached (figure 4.7).[155] The reaction produces stoichiometric amounts of $MnI(CO)_5$ as an easily removed byproduct.

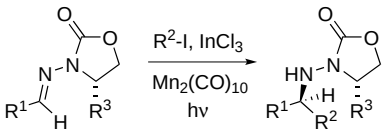


Figure 4.7: The formation of chiral hydrazines by the addition of alkyl radicals to N-acylhydrazones by Friestad and coworkers.

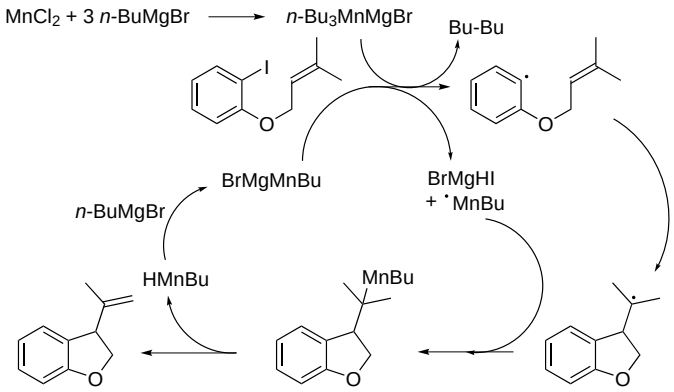


Figure 4.8: The radical cyclization of allyl 2-iodophenyl ether initiated by an *in situ* formed tributylmanganate.

Watanabe,[156] and later Ryu,[157] reported the photocarbonylation of alkyl iodides, forming esters and amides in the presence of alcohols and amines respectively, catalyzed by $Mn_2(CO)_{10}$ under UV irradiation and 1 atm CO. Kinetic studies of the reaction strongly indicates a non-chain radical mechanism.[158]

Manganese(II) and manganese(III) Oshima and coworkers reported the use of catalytic amounts of $MnCl_2$ together with butylmagnesium bromide or butyllithium as stoichiometric reductant to perform cyclizations of allyl 2-iodophenyl ethers. The active reagent is tributylmanganate which forms *in situ* by the reaction of one $MnCl_2$ with three equivalents of butyllithium. Initially the reaction was thought to proceed only with stoichiometric amounts of $MnCl_2$, but the amounts could be reduced to 20 %, using four equivalents of butylmagnesium bromide, as long as oxygen was present in the reaction. The mechanism for the cyclization is shown in figure 4.8. Evidence for the existence of the intermediary organomanganese species was found by trapping this with various electrophiles. The catalytic cycle of the manganese is not completely understood, nor is the role of oxygen quite clear, but without oxygen present the cyclization does not run to an end.[159]

Mn(III) species from the *in situ* oxidation of $Mn(OAc)_2$ to Mn(III) by either reaction with oxygen or electrolysis have been reported as catalytic initiator on several occasions.[160] Otherwise Mn(III) is better known as a stoichiometric one-electron oxidant, used to perform a broad variety of cyclizations and additions of free radicals where the radical is obtained oxidatively by loss of a hydrogen atom, rather than reductively which is the case when for example tributyltin is used to homolytically abstract a halogen atom.[150]

4.2 Mn-catalyzed cross coupling reactions

The reason for the attempted manganese catalyzed Negishi reaction described in the introduction can be found in the general desire to perform cross coupling reactions catalyzed by manganese instead of palladium. The palladium catalyzed cross couplings are among the most important synthetic methods to be discovered in newer times. Their scopes are versatile, the reaction conditions mild and they are employed in uncountable reactions every day. Pd-catalyzed reactions alone accounted for 10 % of the reactions performed in the pharmaceutical industry in 2010 according to a recent study[12] and three of the pioneers in the field of Pd-catalyzed cross-couplings, Heck, Negishi and Suzuki, were awarded the 2010 Nobel prize in chemistry for their contributions. But palladium has some considerable drawbacks, in particular the high price, low abundance and severe toxicity of the element, creating huge incentives to expand the palette of catalysts that are available to the synthetic chemist.

Apart from the catalytic abilities which make palladium indispensable in chemical synthesis, the element also has other properties that makes it quite coveted in several industries. Its rarity and lustrous appearance makes it attractive for use in jewelry; its strength and durability makes it suitable for use in dentistry, as alloys together with gold and silver; and its conductivity and resistance to wear makes it useful in all manner of electronic applications.[161] By far the biggest consumer of palladium though is the car industry which uses the element for autocatalysts and accounts for over 70 % of the total consumption. The annual production of palladium ranges around 300 tonnes, a number that has been more or less constant for many years, but as the demand for the element is ever increasing the price has grown steadily over the last decades, reaching a stunning level of 20.000 $/kg in 2011.[162]

For the pharmaceutical industry what is even more concerning than the high price of palladium is its severe toxicity. Palladium does not occur naturally in the human body and thus all Pd-compounds are considered toxic. The limit for residual metal impurities in orally administered drugs is 10 ppm for palladium, as specified by the European Medicines Agency,[163] but the typical levels of palladium residues after workup of a cross-coupling reaction is in the range of 100–5000 ppm.[164] This poses a huge problem for the drug manufacturers, and creates a demand for alternative purification strategies or even better: New catalysts based on non-toxic metals.

A fair amount of research has been performed on catalysts based on iron,[16] copper[17] and cobalt.[18] They seem good candidates: Capable of catalyzing many of the same reactions as palladium, but more abundant, a lot cheaper and less toxic. The same could be said about manganese, but inexplicably this particular element seems quite overlooked. Manganese exists naturally in the human

body and an average grown-up ingest in the range of 2–9 mg/day from food and water.[165] Thus manganese is a metal of low safety concern and the limit for residual manganese impurities in orally administered drugs is 250 ppm, as specified by the European Medicines Agency.[163] It is the 12^{th} most abundant element in the earths crust, the annual production is around 14.000.000 tonnes and the market price is approximately 3 $/kg. Chemically manganese is one of the most versatile elements in the periodic system and exists in an incomparably broad range of oxidation states, from -3 to +7. Together all these facts constitute a solid good reasoning why manganese would be a good candidate for alternative catalysts for cross coupling reactions.

4.2.1 A brief overview of the literature

The number of papers published on manganese catalyzed cross couplings is negligible compared to the stunning amount of literature and research that exists on their palladium catalyzed counterparts. At the moment the former adds up to only around a dozen papers, several of which are poorly written and offer so little in terms of descriptions of reaction conditions, yields and the exact nature of the catalyst, that they can hardly be used as scientific evidence for the course of the reaction at all. In the current section a brief overview of the literature that exists on the manganese catalyzed cross-couplings and related reactions will be provided.

Kumada coupling The Kumada coupling, the palladium or nickel catalyzed coupling between a Grignard or organolithium reagent and a haloarene or haloalkene, is probably the most well documented cross coupling reaction to be successfully catalyzed with manganese. The reaction is described in four different papers, all four of them utilizing a Mn(II) salt as catalyst under almost identical reaction conditions but on different substrates. The earliest paper is from 1998 from the research group of Gérard Cahiez and describes the coupling of conjugated chloroenynes and chlorodienes with various Grignard reagents.[166] The conditions are very mild: 3 % of $MnCl_2{\cdot}2LiCl$, temperatures at room temperature or lower, THF as solvent and a co-solvent like TMU or DMPU or another tetrasubstituted urea present in 8 %. Substituents on the chloroenyne included pentyl, phenyl, trimethylsilyl, 1-hydroxyethyl and 3-chloropropyl among others. The yields varied from moderate to good depending on the choice of substrate and the best examples gave close to quantitative yields.

The following year the scope of the reaction was expanded to include coupling of aryl halides with Grignard reagents under similar conditions.[167] Aryl magnesium bromides, as well as some primary and secondary alkyl magnesium bromides, were coupled with activated aryl halides, in THF, at 0-20 °C, in

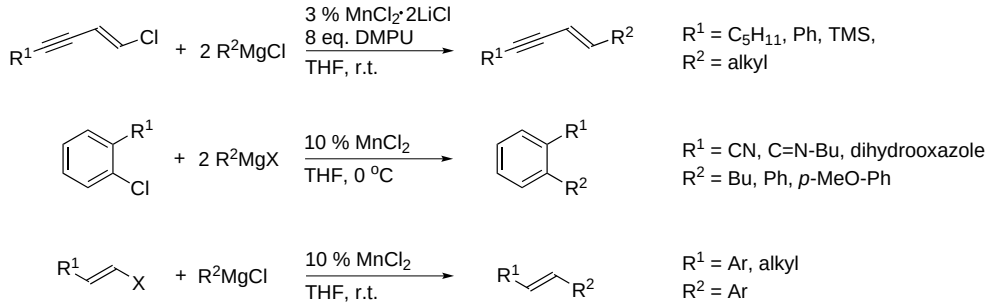


Figure 4.9: The manganese catalyzed Kumada reaction reported by Cahiez and coworkers.

the presence of 10 mol % of $MnCl_2$. The yields were good to excellent. Finally in 2008 the substrate scope of the reaction was more or less completed as the same research group published a paper about the manganese catalyzed coupling between aryl Grignard reagents and alkenyl halides.[168] Again the reaction conditions were almost identical; THF as solvent, temperatures at room temperature or lower, 10 % of $MnCl_2$ and the yields were moderate to good. The general reaction conditions from the three papers are shown in figure 4.9.

Two years prior hereto a paper had been published on the manganese catalyzed coupling of heterocyclic chlorides with alkyl- and aryl magnesium halides by the german chemist Magnus Rueping.[169] Not surprisingly the employed reaction conditions were much the same as the ones used by the Cahiez group, namely in THF at 0–20 °C with 1-5 mol % of $MnCl_2$, giving moderate to good yields of various products.

Buchwald-Hartwig type couplings Another type of reaction that has been reported to work well with manganese catalysts are C-N couplings, similar to the Buchwald-Hartwig reaction, which is the palladium catalyzed coupling of amines with aryl halides. Four papers have been published from 2009–2013, concerning the formation of C–N bonds by the coupling of alkyl or aryl halides with different amines, amides and nitrogen containing heterocycles. Unfortunately the reported results are highly inconsistent and all four papers are by the same research group, which compromises the credibility of the publications.

The first paper describes the coupling between initially iodobenzene and pyrazole, which takes place in the presence of 10 % of $MnCl_2 \cdot 4H_2O$, 20 % of *trans*-1,2-diaminocyclohexane and $K_3PO_4{\cdot}H_2O$(two equivalents) in water at 130 °C.[170] The yield was 78 %, and the reaction conditions were subsequently applied to perform couplings between a range of substituted iodobenzenes with pyrazole in similar yields. Furthermore the exact nature of the manganese

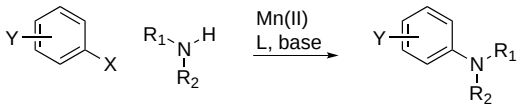


Figure 4.10: The manganese catalyzed Buchwald-Hartwig reaction. X = I, Br. Y = MeO, Me, Cl, Br, F, CF_3. R_1, R_2 = 1° or 2° ; aliphatic, aromatic, heterocyclic. L = *trans*-1,2-diaminocyclohexane, L-proline, TMEDA, DMEDA. Base = $K_3PO_4 \cdot H_2O$, NaO^tBu, K_2CO_3, Cs_2CO_3. Mn(II) = $MnCl_2 \cdot 4H_2O$, $Mn(acac)_2$, $Mn(ClO_4)_2 \cdot H_2O$, MnF_2, $Mn(OAc)_2$, MnO_2. Solvent: Water or DMSO. T = 130 °C.

catalyst seems to be of less importance, as good yields were also obtained when using other Mn(II) salts like $Mn(acac)_2$, $Mn(ClO_4)_2 \cdot H_2O$, MnF_2, $Mn(OAc)_2$ and MnO_2.

The following year the method was expanded to include coupling of aryl halides (primarily iodides but bromides also seem to work) with aliphatic amines.[171] The reaction conditions were slightly different, using L-proline as ligand and potassium *tert*-butoxide as base in DMSO and the catalyst loading was reduced to 5 %, but the yields were still moderate to good with most of the substrates. Again the exact nature of the Mn(II) salt employed seems to be of little importance, and $MnCl_2 \cdot 4H_2O$ was chosen mainly for its low price. It should be noted though that the reaction also runs in the absence of manganese and gives 50 % yield with L-proline and ^{t}BuOK in DMSO.

In 2012 the scope of the reaction was expanded to include coupling of indoles with iodopyridines and iodothiophene.[172] The reaction conditions were identical to those from the 2009 paper, apart from the use of Cs_2CO_3 as the base and the fact that in this reaction the nature of the Mn(II) salt does seem to play a role, as the yields were improved considerably when using MnF_2 as catalyst. The general reaction conditions can be summarized as catalytic amounts of a Mn(II) salt in the presence of an amine ligand and a base, in a highly polar solvent, like H_2O or DMSO at elevated temperatures. The general reaction is shown in figure 4.10.

Recently the group published a similar method for N-arylation of amides and sulfonamides.[173] This time the catalytic system was a mixture of Cu(I) and Mn(II), but otherwise the reaction conditions were the same: *trans*-1,2-diaminocyclohexane as ligand and a base in water at 130 °C gives the desired products in good to excellent yields.

A few critical observations must be attached to the papers described above. In many of the cases the exact nature of the catalyst seems to be of little significance, and in some examples the reaction even runs well without any catalyst present. On the other hand the employed base and ligand seems to be of paramount importance for the yield, but which base or ligand works best changes from one paper to the next. In none of the examples do the

authors report any analysis regarding the purity of the applied reagents. The combination of these facts leads to the obvious suspicion that the reported reactions are actually catalyzed by trace metal impurities; a subject discussed in more detail in section 4.2.3.

Suzuki, Heck, and Stille The absolute superstars of the palladium catalyzed cross coupling reactions must be the three Nobel prize winning name reactions: The Heck–, the Suzuki– and the Negishi reaction, as well as the highly utilized Sonogashira and Stille reactions. Surprisingly hardly any records exist on attempts to perform these reactions with manganese, and the few that do exist are of a somewhat questionably quality.

In a paper from 2000 Iyer and Thakur claims that a Mn catalyst facilitates the Heck reaction.[174] The exact nature of the catalyst is not clear, and the yields and reaction conditions are not given; only a few lines in the text claims that "The Mn catalyst also gave moderate yields of the substituted products from the reactions of different olefins and aryl halides". Apparently the Mn catalyst in question is synthesized by the Urushibara method from $MnCl_2$ with Zn dust. The Urushibara method is a way of producing a very fine powder of a given metal, for use in catalytic reactions. First a salt of the desired metal is dissolved in water, then the metal is precipitated as a fine powder by adding another metal of greater ionization tendency and finally the precipitate is further activated by treating it with aqueous acid or base.[175] From these descriptions it is assumed that the catalyst in question is Mn(0), but with no experimental or analytical data available it is impossible to conclude on the purity of the catalyst or even whether this is the catalyst at all. It might as well be untransformed $MnCl_2$ that is responsible for catalyzing the Heck reaction. No other records exist of attempts to catalyze the Heck reaction by manganese, to the best of our knowledge.

The only published example of a Suzuki reaction catalyzed by a manganese complex is from the Chinese Journal of Catalysis.[176] In a paper from 2008 the authors present the results of a series of Suzuki reactions between arylbromides and phenyl boronic acids, catalyzed by a hydroxyapatite supported manganese catalyst, in low to moderate yields. No structure of the catalyst is given, but its synthesis is described. Hydroxyapatite was synthesized from $Ca(NO_3)_2 \cdot 4H_2O$ and $(NH_4)_2HPO_4$ by the so-called precipitation method,[177] and is subsequently treated with $Mn(OAc)_2$ in aqueous solution to give the utilized catalyst. The active catalyst is assumed to be a Mn(II) complex.

A manganese catalyzed Stille coupling has been reported by Kang and coworkers.[178] The reaction allegedly proceeds impeccably in the absence of palladium, using instead $MnBr_2$ or CuI (10 %) together with NaCl or KCl (one

equivalent) as catalytic system. $MnCl_2 \cdot 4H_2O$ can also be used as catalyst but gives lower yields, whereas MnI_2 does not give the coupled product at all. The solvent is either NMP or DMF, the reaction temperature is 100–120 °C, and the yields are good to excellent. The same research group has subsequently published a paper on the manganese catalyzed cross coupling between organostannanes and hypervalent iodonium salts to give biaryls. In contrast to the previous paper the best catalyst in this case is $MnCl_2 \cdot 4H_2O$, whereas $MnBr_2$ did not work. The reactions run in a mixture of NMP and THF at 70 °C and give good yields.[179] Despite the promising applications of these reactions there have been no publications on the subject in 15 years.

No papers have been published on Mn-catalyzed Negishi or Sonogashira couplings, to the very best of our knowledge.

C-S coupling Yadavalli and coworkers reported a rather efficient coupling of aryl– or vinyl halides with thiols to form sulfides using $MnCl_2 \cdot 4H_2O$ as catalyst. The reactions were performed in DMSO at 110 °C in the presence of 1 % TMEDA and 1.5 equivalents KOH with a catalyst loading of 15 %. The reported yields were good and a variety of different substitution patterns were possible on both the halide and thiol without significant deterioration of the reaction.[180] Very recently though Lee and coworkers claimed that these results must arise from metal impurities in the employed $MnCl_2 \cdot 4H_2O$ or KOH, as repeating the experiments with ultrapure reagents resulted in a markedly diminished yield. They report instead that the use of 20 mol % $MnCl_2$ and 20 mol % 1,10-phenanthroline in toluene at 135 °C gave good to excellent yields of thioethers from the coupling of aryl iodides and thiols.[181]

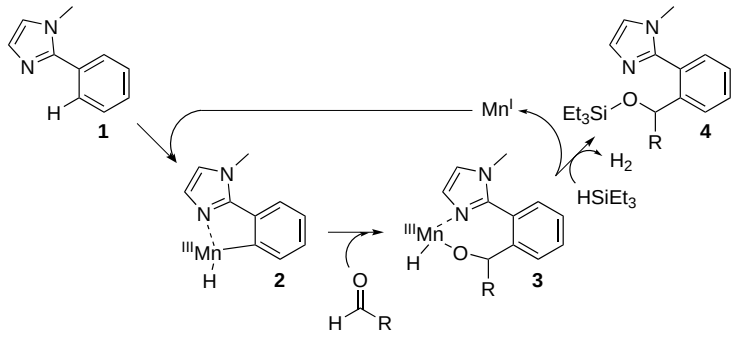


Figure 4.11: The proposed mechanism for the Mn(I) catalyzed insertion of aldehydes to an aromatic C-H bond proposed by Kuninobu and Takai.

$MnBr(CO)_5$ catalyzed reactions In 2007 Kuninobu and Takai reported the use of $MnBr(CO)_5$ as catalyst for the insertion of aldehydes into the ortho C-H bond of imidazolium substituted benzenes. The reaction gives good yields with a variety of aldehydes with 5 mol % of $MnBr(CO)_5$ in refluxing toluene. The proposed mechanism involves first an oxidative addition of Mn(I) into the ortho C-H bond of the imidazolium benzene, forming a Mn(III) complex in which Mn is coordinated to one of the imidazolium nitrogens. Next step is an insertion of the aldehyde into the C-Mn bond, and finally a reductive elimination, mediated by a hydrosilane, releasing the corresponding silyl ether and reforming the active Mn(I) species.[182] The proposed mechanism is shown in figure 4.11. The plausibility of this mechanism is mainly supported by the fact that formation of the possible intermediate **3** in figure 4.11 is observed when using stoichiometric amounts of manganese, before addition of the silane.

The same research group has also reported the use of $MnBr(CO)_5$ as catalyst for the formation of 2-pyranones from the insertion of acetylenes into β-keto esters[183] and for the formation of aromatic compounds from alkynes and 1,3-dicarbonyl compounds.[184]

Nakamura has also reported the use of $MnBr(CO)_5$ for the formation of aromatic compounds from 1,3-dicarbonyl compounds and terminal alkynes, shown in figure 4.12. The reaction is regiospecific and leads exclusively to the formation of 1,2,3,4-substituted aromatic products when an aryl-acetylene is used.[185] At first glance the reaction seems reminiscent of the [2+2+2] cycloaddition of alkynes to form aromatic rings, but a thorough study of the reaction mechanism based on DFT calculations as well as experimental studies strongly suggests otherwise.[186] The first step is similar to a previously reported indium catalyzed addition of enolates to alkynes.[187] The resulting intermediate then

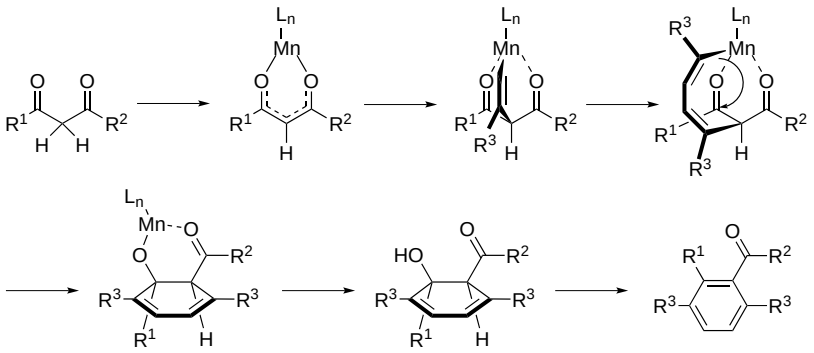


Figure 4.12: The proposed mechanism for the Mn(I) catalyzed formation of aromatic compounds from 1,3-dicarbonyl compounds and terminal alkynes.

adds to another alkyne molecule to form a new intermediate, which cyclizes by a nucleophilic attack on one of the carbonyl groups, forming a cyclohexadienol intermediate which then subsequently eliminates water, leading to the formation of the aromatic ring. The catalytic cycle does not seem to involve any change in the oxidation state of manganese.

Very recently the same complex has been used to accomplish the first manganese catalyzed aromatic C-H alkenylation with terminal alkynes. The reactions run in the presence of an amine base, in diethyl ether at 80–100 °C. The range of alkynes that can be used is rather broad; aromatic as well as aliphatic, and both electrondonating and –withdrawing groups are tolerated. The scope of aromatics used is limited to substituted arylpyridines, but the substituents range widely and contains both electrondonating and –withdrawing groups. The yields of the reported reactions are good. The reaction gives comparable yields when using the Mn(0) complex $Mn_2(CO)_{10}$.[188]

4.2.2 Screening for new reactions

As was rationalized in the previous sections the development of Mn-catalyzed cross coupling reactions would have a huge impact on the field of catalysis in general and the medicinal industry in particular. It is a field that has not been explored to any notable extent apart from a select few reactions, and thus no obvious starting point for the exploration was available. The Suzuki, Heck and Sonogashira reactions are among the most widely employed of the Pd-catalyzed cross couplings and therefore these three reactions were chosen for the initial screenings. As substrates were chosen simple molecules that are known to react well in the classic palladium-catalyzed couplings: Iodobenzene with phenyl boronic acid, styrene and phenyl acetylene respectively.

In order to be able to screen a large number of reactions at the same time an experimental setup was used consisting of threaded vials made from thick-walled glass with fitting screw caps. The vials could be placed into an aluminium block with nine holes matching the diameter of the vials and thereby be heated efficiently to the desired temperature without risk of the vials exploding and sending shards all over the laboratory. Two identical setups allowed for the screening of up to 18 reactions at a time, and the closed vials made it possible to run the reactions at a higher temperature than the reflux temperature of the solvent - at least until a certain point where the internal pressure simply causes the solvent to evaporate through minuscule leaks between the thread and the cap. One possible drawback of the setup is that a relatively high pressure builds up in the vials during the reaction, which may be counterproductive for some reactions, depending on the mechanism. The reactions were monitored by GC/MS.

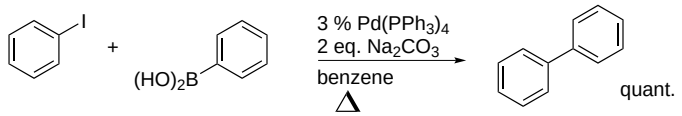


Figure 4.13: The reaction between iodobenzene and phenyl boronic acid, chosen as test substrates, gives quantitative formation of biphenyl under classic Suzuki reaction conditions.

The Suzuki reaction As substrates for the initial testing of a manganese catalyzed Suzuki reaction was chosen iodobenzene and phenyl boronic acid. The reaction between these two substrates gives quantitative formation of biphenyl after three hours under classic Suzuki conditions, shown in figure 4.13. To screen the reaction with manganese the same substrates were reacted in the presence of 20 mol % of $MnCl_2$ in eight different solvents (toluene, water, THF, ethanol, heptane, DMF, acetonitrile, DCM), with and without two equivalents of aqueous Na_2CO_3 and at two different temperatures, 100 and 150 °C, respectively. No formation of biphenyl was observed in any of the reactions.

A new screening was then performed, running the reaction in the presence of 20 mol % of $Mn_2(CO)_{10}$ and one equivalent of Et_3N, with and without PPh_3 present, in four different solvents (toluene, water, THF and ethanol) at 150 °C. In the reactions in toluene peaks arising from other than the starting material was now observed. A tiny peak from biphenyl was present, but as this also appeared in a similar setup for the Heck reaction it most likely arises from the homocoupling of iodobenzene and not from the coupling between one iodobenzene and one phenyl boronic acid. Three larger peaks, all with a m/z of 168, were present. This mass corresponds to the coupling of iodobenzene with toluene, and the three different peaks arise due to the presence of both ortho-, meta- and parasubstitution. This reaction most likely happens by a radical mechanism, as $Mn_2(CO)_{10}$ is known to be a radical initiator, with an affinity for abstracting halogen atoms.[155] Abstraction of an iodo-radical from iodobenzene creates a phenyl radical which can couple to a toluene or an iodobenzene molecule forming phenyltoluene or biphenyl, respectively.

From a quick preliminary screening of the reaction conditions the best setup to achieve this particular transformation was found to be heating iodobenzene to 150 °C in the presence of 20 mol % of Et_3N, 20 mol % of $Mn_2(CO)_{10}$ and 40 mol % of PPh_3 in toluene, which provided phenyltoluene in a yield of approximately 15 % by GC analysis.

The Heck reaction As substrates for the screening of the Heck reaction was chosen styrene and iodobenzene, which couples to give good yields of stilbene under classic Heck reaction conditions, shown in figure 4.14. To screen the

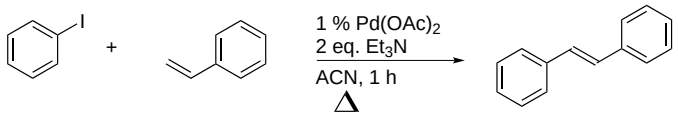


Figure 4.14: The reaction between iodobenzene and styrene, chosen as test substrates, gives good yields of stilbene under classic Heck reaction conditions.

reaction with a manganese catalyst the reaction was run in the presence of 20 mol % of $MnCl_2$ in eight different solvents (toluene, water, THF, ethanol, heptane, DMF, acetonitrile, DCM), with two equivalents of Et_3N, with and without PPh_3 present. The reaction was screened at two different temperatures, 100 and 150 °C. At 100 °C no reaction was observed in any of the solvents. At 150 °C in toluene in the presence of PPh_3 the formation of two different cis/trans isomers of 1,4-diphenylbutadi-1,3-ene was observed.

In complete analogy to the Suzuki reaction the Heck reaction was also screened in the presence of 20 mol % of $Mn_2(CO)_{10}$ and one equivalent of Et_3N, with and without the presence of PPh_3, in four different solvents (toluene, water, THF and ethanol) at 150 °C. As was also observed for the Suzuki reaction, a tiny peak for biphenyl from the homocoupling of iodobenzene as well as a peak for phenyltoluene from the coupling of iodobenzene and toluene were observed when the latter was used as solvent. In addition hereto tiny amounts of transstilbene was observed when the reaction was run in either toluene, THF or ethanol. The formation of small amounts of diphenyl ketone, probably from the insertion of CO to biphenyl, was also observed in these three solvents.

The Sonogashira reaction The coupling between iodobenzene and phenyl acetylene to give diphenylacetylene was chosen as a model system for screening of the Mn-catalyzed Sonogashira reaction. The reaction gives quantitative yields under classic Sonogashira reaction conditions, shown in figure 4.15. The initial attempts to catalyze this reaction with manganese was without a copper co-catalyst; just 20 % of $MnCl_2$, two equivalents of Et_3N, with and without PPh_3 present. The reaction was screened in eight different solvents (toluene, water, THF, ethanol, heptane, DMF, acetonitrile, DCM), and at two different temperatures, 100 and 150 °C.

In water in the presence of PPh_3 at 150 °C, tiny peaks for the formation of diphenylacetylene was observed, along with stilbene, styrene and ethylbenzene. Otherwise no formation of product was observed. Changing the ligands did not change the outcome of the reaction.

When CuI was added as co-catalyst some formation of diphenylacetylene occured. The highest yield was around 20 % and was obtained in the presence of PPh_3, using THF as solvent. Screening of different ligands and bases resulted

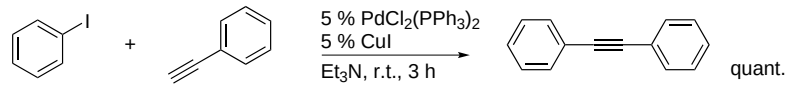


Figure 4.15: The reaction between iodobenzene and phenyl acetylene, chosen as test substrates, gives quantitative formation of diphenylacetylene under classic Sonogashira reaction conditions.

in an optimized yield of around 25 % when using P(*o*-tol)$_3$ as ligand and Et_3N as base. The reaction also occured in the presence of CuI without $MnCl_2$ present, although with slightly lower yields. The purity of the CuI was not tested and therefore contamination with palladium or other metals is quite probable. The reaction was also tested by employing $MnBr(CO)_5$ as catalyst in 20 mol % loading, with and without CuI present, but resulted in no formation of the product in any of the cases.

Just as for the Suzuki and the Heck reaction the Sonogashira reaction was screened in the presence of 20 mol % of $Mn_2(CO)_{10}$ and one equivalent of Et_3N, with and without addition of PPh_3, in four different solvents (toluene, water, THF and ethanol) at 150 °C. The reactions were run with and without CuI present as co-catalyst. As would be expected from the previous reactions, the reactions running in toluene produced small amounts of phenyltoluene. In addition hereto tiny peaks for the formation of transstilbene were observed when running the reaction in the presence of PPh_3 using either toluene, THF or ethanol as solvent. The formation of transstilbene can be explained by a radical reaction: Addition of a phenyl radical, from the abstraction of iodine from iodobenzene, to the β-position of phenylacetylene would result in the formation of a transstilbene radical which can then abstract a hydrogen from the solvent. The mechanism is analogues to the one reported by Chen and Guo[144] described in section 4.1.2. In none of the reactions were diphenylacetylene observed as product.

4.2.3 Validating the literature

As all of the preliminary attempts to make the Suzuki, Heck and Sonogashira reactions work proved unfruitful the attention was instead turned toward some of the literature examples, i.e. the Stille and the Kumada reaction, in order to gain a deeper insight to some of the reactions that allegedly work with a manganese catalyst. As will be elaborated in the current section it proved impossible to reproduce the results from the paper on the Mn-catalyzed Stille reaction by Kang and coworkers, while the results from the papers on the Mn-catalyzed Kumada reaction, with some reservations, seem valid enough.

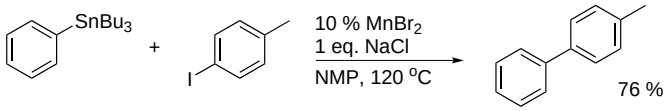


Figure 4.16: According to the 1997 paper by Kang and coworkers the reaction between tributyl(phenyl)stannane and 1-iodo-4-methylbenzene should give 4-phenyltoluene in 76 % yield under the shown conditions.

The Stille reaction As was described in section 4.2.1 Kang and coworkers have reported a manganese or copper catalyzed Stille reaction between vinyl, phenyl or heteroaryl tributylstannanes and vinyl or aryl iodides.[178] According to this paper the reaction between tributyl(phenyl)stannane and 1-iodo-4-methylbenzene should give 4-phenyltoluene in 76 % yield with $MnBr_2$ and 81 % yield with CuI when following the published procedure. The reaction is shown in figure 4.16. It was attempted to reproduce the reaction by following the procedure from the supporting information. NMP was drawn from a recently opened sure-seal bottle and $MnBr_2$ and NaCl were bought from Sigma Aldrich and opened immediately prior to use. The tributyl(phenyl)stannane and 1-iodo-4-methylbenzene employed were of an older date, but performed well in a Stille reaction under classic conditions: In the presence of 1 % of $Pd(PPh_3)_4$ in NMP at 90 °C the two reagents coupled to give the expected product in a fair amount as observed by GC/MS. The Kang procedure was repeated twice with the same result: No conversion of the starting material was observed by GC/MS.

As the paper also provides a procedure for a copper catalyzed Stille reaction this was attempted as well. According to the paper the reaction conditions are the same as for the manganese catalyzed procedure, also employing one equivalent of NaCl in NMP at 110 °C, but with 10 % of CuI instead of 10 % of $MnBr_2$. Two identical experiments were set up, the only difference being that one was with CuI from a bottle opened immediately prior to use, whereas the other was with CuI from an old bottle on the shelf. None of the reactions showed any formation of the product by GC/MS.

These results drew attention to some critical points in the paper: It can be noticed that while it is mentioned that two kinds of CuI can be used, one 99.999 % from Aldrich Chem. Co. and one 98 % from Janssen Chimica, no mention is made of the origin or purity of neither the $MnBr_2$ nor the NaCl, KCl, LiCl, KF, nor CsF which are added in equimolar amounts. Several different manganese salts are tested, showing that the reaction works with $MnBr_2$ and $MnCl_2 \cdot 4H_2O$, but not with MnI_2. The text does mention though, that "The yields of the coupled product ... are highly dependant on the salts employed" and "The addition of NaCl was crucial in these cross-couplings". No experiment

seems to have been performed where the reaction is run without the addition of manganese or copper but with the rest of the experimental setup unchanged, so it cannot be ruled out that for example the NaCl and KCl are contaminated with palladium and thus that the addition of these salts in equimolar amounts provides enough palladium for the reaction to work.

A note on trace metal impurities Without accusing anybody of anything this would not be the first example of a faulty claim of a reaction to run in the absence of palladium, when in reality it is catalyzed by trace amounts of the metal. One famous example is the declared "Transition-Metal-Free Suzuki-Type Coupling" reported in 2003 by Leadbeater and coworkers.[189] In the paper a Suzuki-type coupling between a range of aryl halides and phenylboronic acid is reported to proceed in good yields in the presence of 3.8 equivalents of Na_2CO_3 and one equivalent of TBAB in water under microwave irradiation. The authors claim that they used new glassware, apparatus, reagents and spatulas. Reagents from several suppliers were used and gave the same results. Furthermore the crude reaction mixtures were analyzed for palladium, nickel, platinum, copper and ruthenium, and the results showed no contamination of these metals above the level of detection for the apparatus, which was 0.1 ppm for palladium and 1.0 ppm for the other metals. On the grounds of these results the authors conclude that the reaction is indeed transition metal free. They note that in the absence of base no reaction occurs at all, and a screening of a wide range of group I and II metal carbonates of similar basicity show that only with Na_2CO_3 and Cs_2CO_3 are the yields acceptable; with the other salts little or no product formation is observed. Other sodium salts are screened as well and show the same low activity. From these results the authors conclude that both the nature of the cations and anions are important, although the exact role of the base is not understood.

Two years later the same research group published a reassessment of their former procedure.[190] Reports about Heck reactions being performed with "homeopathic amounts" of palladium[191] had prompted the research group to perform an even more thorough analysis of all the involved reagents by ICP-MS. Analysis of solutions of so-called ultrapure Na_2CO_3 in ultrapure water gave palladium concentrations in the range of 20–50 ppb. These levels of palladium were found in many commercially available sources of Na_2CO_3 but not in K_2CO_3, which would explain why the reactions work with one base but not with the other. The authors conclude that the reactions formerly reported to be transition metal free are instead reactions that are catalyzed by palladium concentrations as low as 50 ppb.

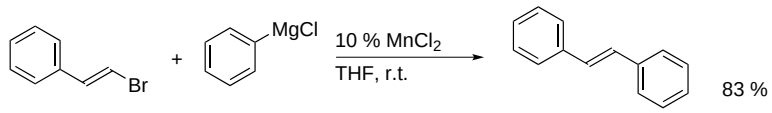


Figure 4.17: According to the 2008 paper by Cahiez and coworkers the reaction between β-bromostyrene and phenylmagnesium chloride should give transstilbene in 83 % yield under the shown conditions.

The Kumada reaction As was mentioned in section 4.2.1 four different papers on a manganese catalyzed Kumada-type coupling have been published. In the 2008 paper by Cahiez and coworkers the coupling between β-bromostyrene and phenylmagnesium chloride (figure 4.17) was reported to proceed in 83 % yield when mixing the reagents in the presence of 10 % of $MnCl_2$ in THF at room temperature.[168] This reaction was chosen as test reaction in the attempts to validate this procedure. It was repeated with a few alterations compared to the published procedure: Firstly phenylmagnesium bromide was used instead of the chloride, as the former was available as stock reagent; secondly anhydrous $MnCl_2$ was used directly from the bottle, instead of dehydrating $MnCl_2 \cdot 4H_2O$ in an oven under vacuum as is described in the experimental procedure from the paper and thirdly the reaction was performed under an argon atmosphere and not nitrogen. Only a trace of product was observed by GC/MS after three hours. Increasing the reaction temperature to 50 °C after addition of the PhMgBr in an otherwise identical experiment resulted in nearly full conversion of β-bromostyrene and formation of transstilbene as the major product, observed by GC/MS.

A very recent paper claims to perform Kumada reactions at 110 °C with no transition metals present at all.[192] Since none of the papers by either Cahiez or Rueping regarding the manganese catalyzed Kumada-type coupling report any experiments where the reactions are run in the absence of a catalyst this seemed like an obvious experiment to perform. Therefore an experiment was conducted, reacting β-bromostyrene and phenylmagnesium bromide in THF at 50 °C, but with no catalyst present at all. This resulted in the formation of some transstilbene, although clearly to a lesser extent than in the presence of $MnCl_2$. The consumption of starting material was nowhere near completion, and also the formation of biphenyl as byproduct was much more pronounced. Still this gives a general idea about a reaction which is performed willingly even in the absence of a catalyst, but which is greatly enhanced by the presence of manganese.

Obviously care should still be taken before proclaiming any of these reactions palladium free, particularly in the light of the examples from the previous section. No analysis of reagents or reactants are reported in any of the pa-

pers, and none were performed in this current study either. This being said the manganese catalyzed Kumada-type reaction seems by far the most promising candidate as starting point for a further study of the manganese catalyzed cross couplings in general.

4.2.4 Final attempts

The Negishi reaction So far the Kumada reaction seemed to be the only manganese catalyzed cross-coupling reaction to show any real promise. One possible explanation for this might be that it requires a very strong nucleophile, in this case a Grignard reagent, in order to transmetalate with the oxidative addition product from $MnCl_2$ and the halide - assuming that the reaction mechanism is the same as for a regular Kumada coupling. If this was the case there would be a fair chance that the Negishi reaction might work under similar conditions, as the organozinc reagent employed in a Negishi reaction in many ways is similar to a Grignard reagent, regarding nucleophilicity, basicity and reductive abilities.

As substrates were chosen the reaction between iodobenzene and *p*-tolylzinc iodide. This reaction works well under regular Negishi conditions: With 5 % of $Pd(PPh_3)_4$ in THF at room temperature the reaction gave nearly quantitative formation of the coupling product by GC/MS. In the absence of palladium though no coupling product was observed. The reaction was tested with both $MnCl_2$ and $Mn_2(CO)_{10}$, 20 % loading in both cases, with and without PPh_3 present, at both room temperature and at 100 °C in THF as solvent. The only product observed in any notable yield was di-*p*-tolylmethanone from CO insertion between two molecules of *p*-tolylzinc iodide in the reactions where $Mn_2(CO)_{10}$ was used as catalyst at elevated temperatures.

Attempting to imitate the manganese catalyzed Kumada reaction to a higher extent a new set of substrates were chosen. This time β-bromostyrene was reacted with *p*-tolylzinc iodide because β-bromostyrene performed well in the Kumada reaction. This new reaction was run in the presence of 30 % of $MnCl_2$ in NMP as solvent. A tiny peak of something with a m/z of 174 was observed, but the peak was so small that initially no attention was paid to it. It was hypothesized that maybe the reducing ability of the Grignard reagent was an important factor in making the Kumada reaction work and therefore the Negishi reaction was performed again with 25 % of $MnCl_2$, but this time the reaction was initiated with the addition of 25 % of PhMgBr before addition of the organozinc reagent, and the solvent used was THF. After refluxing overnight a large peak with m/z 174 and considerable consumption of β-bromostyrene was observed. Isolation and NMR of the compound proved this to be 2-styryltetrahydrofuran from the reaction between β-bromostyrene and THF, and the increase in for-

mation of this product was not due to the addition of the Grignard reagent, but due to the change of solvent to THF. The origin of THF in the first reaction was from the *p*-tolylzinc iodide which is a 0.5 M solution in THF.

Conclusive remarks As was explained in the introduction to this chapter this unexpected reaction was assessed to be interesting enough to spend some time trying to optimize the conditions and explore the scope and limitations of the methodology. That process is described in the following sections. This decision took the current project along an unexpected trajectory and due to the limited time at hand put a rather abrupt end to the further exploration of the manganese catalyzed cross coupling reactions. This does not mean of course that this area of research holds no promise at all: What has been described in the current section is only a very brief preliminary screening of possible reactions and a more thorough study would likely reveal more interesting knowledge and possibly pave the way for the discovery of new reactions.

Still some conclusions can be drawn from the experiments described above. Firstly it seems apparent that it is not possible to just exchange palladium for manganese without changing any other reaction conditions and still achieve the same reaction. Obviously, one might add, as it seems likely that such a simple experiment may already have been performed many times by other researchers, to the same end - without anybody ever knowing about it. Secondly a great care and consideration must be given to the purity and exact identity of the reagents used and the analysis of these ought to be a mandatory part of any publication claiming to perform new catalytic reactions. Most of the papers issuing claims about new catalytic reactions provide no information of the sort and in general exhibit a great carelessness in the experimental and mechanistic validation of the reaction at hand. Thus, it is not unlikely that most of the published procedures employing a manganese catalyst to perform some coupling reaction is in fact a case of a reaction catalyzed by trace metal impurities in some of the reagents or in the catalyst itself.

An obvious starting point for further research in this area would be to repeat the published procedures with ultrapure reagents, thus consolidating whether the reactions are indeed catalyzed by the claimed reagents or by impurities present herein. Next step would be a mechanistic investigation of one or more of the reactions that actually do work. Determination of the actual reaction mechanism would provide valuable information for the design of new reactions and give a good idea about which reactions it would be feasible to try to perform with manganese and which are more of a long shot.

4.3 Method development

The formation of 2-styryltetrahydrofuran by the reaction of a tetrahydrofuryl radical with β-bromostyrene, shown in figure 4.18, was discovered serendipitously when attempting to perform a manganese catalyzed Negishi reaction as described in the previous sections. The current section describes the optimization of the reaction conditions as well as the exploration of the scope and limitations of the method. A variety of cyclic- and acyclic ethers as well as cycloalkanes and a cyclic amine were used as radical precursors instead of THF and a range of substituted β-bromostyrenes were applied as substrates in the reaction.

4.3.1 Optimization of reaction conditions

Radical initiator Since the combination of *p*-tolylzinc iodide and manganese chloride is a rather exotic mixture of reagents the first step in the development of a new synthetic method was to find a more common, and possibly also cheaper, method of generating the reactive radical, hopefully obtaining a higher yield in the process. Omitting the $MnCl_2$ reduced the yield to 13 %, stressing the importance of manganese in combination with the zinc reagent (entry 2, table 4.1).

It is known from the literature that benzoyl peroxide can be used for the formation of THF radicals, as this was the reported reagent in what is believed to be a quite similar addition-elimination of tetrahydrofuranyl radicals to β-nitrostyrene reported by Yao and coworkers.[145] Applying their reaction conditions and adding three equivalents of Bz_2O_2 resulted in only 6 % formation of the desired product (entry 3), and though addition of $MnCl_2$ increased the yield to 35 % (entry 4) this was still nowhere near the yield from the original setup. Apparently the formation of the THF radical is not the only prerequisite for the formation of the product. Compared to the very electron withdrawing substituent on nitrostyrene, which renders the double bond highly electron deficient and thus apparently quite available for attack by a nucleophilic radical, the bromo-substituent on the β-bromostyrene is only weakly electron withdrawing. It would appear that the zinc reagent plays a double role, acting both as

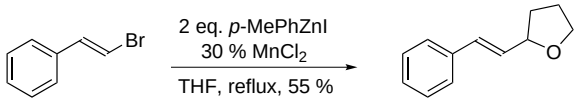


Figure 4.18: The formation of 2-styryltetrahydrofuran by the reaction of β-bromostyrene and THF in the presence of 2 eq. *p*-tolylzinc iodide and 30 % of $MnCl_2$.

a radical initiator and as a Lewis acid activating the styrene for a nucleophilic radical attack. The fact that the yield is improved when using $MnCl_2$ in combination with Bz_2O_2 suggests that manganese also plays a role in the activation of the substrate towards nucleophilic attack.

Use of the radical initiator AIBN, with or without $MnCl_2$ present, resulted only in traces of the desired product (entries 5 & 6). Use of the combination Et_3B/air did give 12 % of the desired product, but accompanied by a comparable amount of 1-phenylbut-1-ene (2) from the addition-elimination of an ethyl radical. The mechanism for Et_3B/air initiated radical reactions commences with the reaction of Et_3B with triplet oxygen thereby releasing an ethyl radical. Apparently under these conditions the addition-elimination of the formed ethyl radical to β-bromostyrene competes with the abstraction of a hydrogen from THF.

The theory that zinc was somehow necessary for the reaction to run needed to be tested further and therefore several easily available zinc reagents were employed in combination with $MnCl_2$ as initiator (entries 8–10). The use of $ZnCl_2$ gave no product at all. PrZnBr, which was the analogue closest resembling the original initiator *p*-MePhZnI, gave a mere 11 % yield and the use of Et_2Zn gave 5 % of the desired product in combination with some 1-phenylbut-1-ene. The mechanism for radical initiation by diethylzinc and air is believed to be analogues to the the Et_3B/air mechanism[142] and with that in mind the observed results are not so surprising after all.

The use of Me_2Zn/air as initiator, even in the absence of $MnCl_2$, gives 33 % yield at room temperature (entry 11) and raising the temperature to reflux (66 °C) results in the formation of 45 % (entry 12). The addition of $MnCl_2$ increases the yield to 67 % (entry 13). One theory about why Me_2Zn works while Et_2Zn does not is presented by Tomioka and coworkers.[141] They hypothesize that the low stability of the methyl radical compared to the ethyl radical causes the former to react immediately with whatever molecule it first encounters, whereas the latter is more long-lived and thus will have a tendency to react with the more reactive substrate. In the very dilute reaction mixtures used, Me_2Zn exclusively abstracts a hydrogen from THF, leaving only tetrahydrofuryl radicals to react with the β-bromostyrene.

All of the attempts to reduce the amount of Me_2Zn were unsuccessful as they resulted in a significant lowering of the yield (entries 14–16). One explanation might be that the mechanism is similar to the one presented by Oshima and coworkers for the radical cyclization of allyl 2-iodophenyl ethers, described in section 4.1.3 and shown in figure 4.8.[159] Here catalytic amounts of $MnCl_2$ reacts with three equivalents of butyllithium or butylmagnesium bromide, forming a tributylmanganate which is the active catalyst. If a similar mechanism is in play in this reaction then the addition of at least three equivalents of the

organometallic reagent is of paramount importance, whereas addition above this point should have no influence on the yield.

Regarding the amount of added $MnCl_2$, increasing it above 30 mol % decreased the yield, whereas a slight lowering of the amount, to 10-15 mol % increased the yield to a maximum of 79 %. Unfortunately, these results proved hard to reproduce and in general the observed yield was around 71 %. The reaction does not require stoichiometric amounts of $MnCl_2$ in order to exhibit optimal performance.

Other attempts to improve the reaction conditions included slow or portionwise addition of Me_2Zn, heating the reaction mixture to reflux temperature before adding Me_2Zn, ensuring very low levels of water in the solvent, running the reaction under argon and raising the reaction temperature by substituting half of the THF with toluene, but nothing seemed to have any effect on the yield.

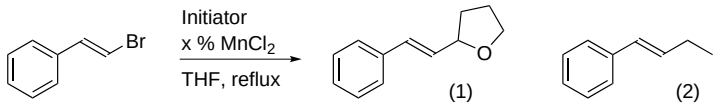


Table 4.1: Testing different radical initators. Unless otherwise stated the reactions were run overnight in refluxing THF under an argon atmosphere.

Entry	Initiator	Eq.	Additive	GC Yield	Comments
1	*p*-MePhZnI	2	$MnCl_2$, 30 %	55 %	
2	*p*-MePhZnI	2	—	13 %	
3	Bz_2O_2	3	—	6 %	
4	Bz_2O_2	3	$MnCl_2$, 12 %	35 %	Open condenser.
5	AIBN	3	—	Traces	
6	AIBN	3	$MnCl_2$, 30 %	Traces	
7	Et_3B & air	3	—	12 %	Formation of (2)
8	$ZnCl_2$	2	$MnCl_2$, 25 %	—	
9	PrZnBr	2	$MnCl_2$, 30 %	11 %	
10	Et_2Zn	3	$MnCl_2$, 30 %	5 %	Formation of (2)
11	Me_2Zn	3	—	33 %	Open condenser, r.t.
12	Me_2Zn	3	—	45 %	Open condenser.
13	Me_2Zn	3	$MnCl_2$, 30 %	67 %	Open condenser.
14	Me_2Zn	2	$MnCl_2$, 40 %	56 %	Open condenser.
15	Me_2Zn	1.5	$MnCl_2$, 35 %	31 %	Open condenser.
16	Me_2Zn	1	$MnCl_2$, 35 %	31 %	Open condenser.
17	Me_2Zn	3	$MnCl_2$, 10 %	79 %	Open condenser.

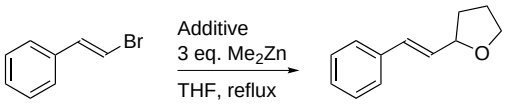


Table 4.2: Testing different Additives. The reactions were run in the presence of O_2.

Entry	Additive	Amount	GC Yield
1	$MnCl_2$	10.5 %	71 %
2	$MnBr_2$	11.8 %	62 %
3	$Mn(OAc)_2$	11.0 %	43 %
3	$Mn(OAc)_3$	11.0 %	75 %
4	$MnBr(CO)_5$	10.8 %	58 %
5	$Mn_2(CO)_{10}$	10.6 %	60 %
6	$FeCl_2{\cdot}4H_2O$	28.5 %	21 %
7	$FeCl_3$	31.0 %	28 %
8	$CuCl_2$	12.8 %	49 %
9	$CoCl_2$	10.0 %	73 %
10	$CrCl_2$	19.6 %	62 %
11	NaCl	18.6 %	28 %

Additives Different metal salts and complexes were tested to see whether the reaction is specific for manganese or if it is a general reaction. The results are shown in table 4.2. In general all the manganese compounds, apart from $Mn(OAc)_2$, increase the yield compared to the reaction with no additive present at all, which gave 45 % (entries 1–5). The best yields are obtained with $MnCl_2$ and $Mn(OAc)_3$. It should be noted that while the use of $Mn_2(CO)_{10}$ gives only 60 % yield, there was full consumption of starting material, but no other products were observed by GC/MS. The $^{\bullet}Mn(CO)_5$ formed by homolysis of $Mn_2(CO)_{10}$ is known to have a strong affinity for abstracting halogens,[155] and therefore a competing mechanism when employing this complex might be the formation of a β-styryl radical which may fragment and terminate, yielding products which are not detected by GC/MS.

Both cobalt(II) and chromium(II) chloride gave yields comparable to the manganese salts (entries 9 & 10), which may not be surprising as both of them are low-valent paramagnetic first row transition metals. Cobalt and chromium are not unheard of in radical reactions: The M(0) carbonyl complexes $Co_2(CO)_8$ and $Cr(CO)_6$ have been applied as catalyst precursors in the Kharasch reaction[193] and the Cr(II) complex $CpCr(CO)_3H$ has been employed as catalyst for some radical cyclizations.[194]

Copper(II)chloride seems to give only a slight improvement of the yield compared to the reaction with no additives (entry 8) and the use of iron chlorides

(entries 6 & 7) and sodium chloride (entry 11) resulted in an actual decrease of the yield.

Not surprisingly, the use of palladium(II) in combination with Me_2Zn resulted in full conversion of the β-bromostyrene to the Negishi coupling product (*E*)-prop-1-en-1-ylbenzene (not shown in the table).

4.3.2 Radical precursors

The scope and limitations of the reaction was tested by applying the methodology to a variety of different radical precursors. The reaction between β-bromostyrene and THF proceeds very well according to GC analysis. With the applied conditions the consumption of β-bromostyrene is around 90 % and the yield of the coupled product ranges from 71-79 %. The disappearance of β-bromostyrene was monitored while applying the procedure to other cyclic ethers, and high levels of consumption was observed. Acyclic ethers and cycloalkanes were also tested, but low levels of starting material conversion were observed. The reaction and the results are shown in table 4.3.

The reaction between β-bromostyrene and THF was scaled up two times compared to the screening conditions, in order to isolate and identify the products. The isolated yield proved to be only 33 %, which was low considering that the GC yields from the screening experiments was 71–79 %. Increasing the amount of Me_2Zn to four equivalents increased the isolated yield to 47 %. Full conversion seemed to have been reached, as there was no starting material present in the crude product, which makes it difficult to explain the low isolated yield. Formation of byproducts may have occurred, but if that was the case then they would be small low-boiling molecules which can not be observed by GC/MS and most likely would evaporate from the reaction mixture under the reaction conditions. The graph correlating the yield of the reaction with the internal standard may be subject to uncertainties and therefore the yields obtained from the GC analysis may be higher than the actual yields. The work-up procedure may be faulty or the scale up of the process may simply render it less efficient, thus giving remarkably lower yields than what was observed on a smaller scale.

Similar problems were experienced with many of the other reactions: The conversion of β-bromostyrene was good from GC analysis and large peaks from formation of the product were observed, but the isolated yields were far from impressive. In many of the cases the yields were improved considerably by increasing the amount of Me_2Zn to four equivalents and these are the yields provided in table 4.3 unless otherwise is noted.

Cyclic ethers Initially the focus was on other cyclic ethers, as it seemed likely that they would behave in a manner similar to THF. 2-Methyltetrahydrofuran (entry 2) initially gave a low conversion, only around 25 %, but a peroxide test revealed peroxide levels of 2 mg/l, which may effectively have quenched the reaction. When the experiment was repeated using a bottle of 2-methyltetrahydrofuran which was opened immediately prior to use, full conversion was observed. Three different products were observed by GC/MS. By far the most abundant species arise from reaction of the precursor at the 2-position, giving (*E*)-2-methyl-2-styryltetrahydrofuran. Two small peaks of equal intensity correspond to the two different diastereomeric forms of (*E*)-2-methyl-5-styryltetrahydrofuran from the reaction of the precursor at the 5-position. These results reveal that the formation of the more stable radical (the more highly substituted) is preferred over formation of the more sterically accessible radical. The most abundant isomer, from the reaction at the 2-position of 2-methyltetrahydrofuran, was isolated in 65 % yield.

THP gave full conversion with three equivalents of Me_2Zn (entry 3). From the GC/MS three different peaks with the correct mass of 188 were observed, most likely arising from the three different possible isomers of the product, from radical formation at the 2–, the 3– and the 4-position respectively. Upon scale-up and workup the most abundant isomer, from the reaction at the 2-position, was isolated in only 28 % yield. By increasing the amount of Me_2Zn to four equivalents an isolated yield of 40 % was obtained. The less abundant isomers could not be separated from each other so none of them are identified, but they seem to be present in around 10 % yield for both of them combined.

1,4-Dioxane only gave 58 % conversion (entry 4) with the use of three equivalents of Me_2Zn, but increasing the amount to four equivalents resulted in 77 % conversion and six equivalents gave full conversion. The explanation for the need for these large amounts of Me_2Zn may be found in the difference in the ease by which the two radicals are formed: The BDE for the tetrahydrofuran-2-yl–H bond is 385 kJ/mol whereas it is 441 kJ/mol for the 1,4-dioxan-2-yl–H bond.[195] Upon scale-up and workup using four equivalents of Me_2Zn the product was isolated in 44 % yield.

1,3-Dioxolane gave 75 % conversion with three equivalents of Me_2Zn, but also here the conversion could be increased by increasing the amount of added Me_2Zn: With four equivalents the conversion was 83 % (entry 5). 1,3-Dioxolane gave rise to two different products, corresponding to radical formation at the 2– and the 4-positions respectively. Upon acidic workup the product from addition-elimination of the 2-radical was hydrolyzed to give cinnamaldehyde (and ethylene glycol) whereas the product from addition-elimination of the 4-radical did not hydrolyze to give 4-phenylbut-3-ene-1,2-diol (and formaldehyde). After acidic workup the product from the radical formation at the 4-position

could be isolated in 16 % yield, whereas alkaline workup made it possible to isolate the product from the radical formation at the 2-position in 31 % yield, although it was difficult to isolate the compound without a slight contamination of the 4-substituted byproduct.

2-Methyl-1,3-dioxolane gave 82 % conversion when running the reaction with three equivalents of Me_2Zn (entry 6) and, as was the case for its parent compound 1,3-dioxolane, products from radical formation at both the 2- and the 4-position were observed. In this case though only trace amount of the latter was observed and the main product (*E*)-2-methyl-2-styryl-1,3-dioxolane was isolated in 34 % yield. In contrast to the unsubstituted 1,3-dioxolane apparently the difference in stability of the two possible radicals is quite large, giving rise to preferentially one product. No attempts to increase the yield by increasing the amount of Me_2Zn has been made with this reaction so far.

3,3-Dimethyloxetane was also attempted applied as radical precursor (not shown in the table). With four equivalents of Me_2Zn full conversion of β-bromostyrene was obtained, but when the reaction mixture was analyzed by GC/MS the chromatogram was a veritable forest of peaks and none of them showed the correct m/z for the desired product. 3,3-Dimethyloxetane is a four-membered ring, which causes a relatively high level of molecular strain compared to for example THF, and renders the molecule prone to ring-opening and polymerization under the right reaction conditions.[196] This reactivity could well be the explanation for the observed deviation from the general trend when employing this particular precursor in the reaction.

Other precursors Diethyl ether gave 56 % conversion with three equivalents of Me_2Zn and an increased conversion of 64 % with four equivalents of Me_2Zn (entry 7). Upon scale-up and workup the product was isolated in 69 % yield. Diisopropyl ether was expected to show higher conversion of starting material, as the formed radical on a tertiary carbon atom should be more stable than the radical on the secondary carbon atom in diethyl ether, but the conversion of starting material was only 31 % and the isolated yield after workup only 12 % (entry 8).

N-Methylpyrrolidine was applied as radical precursor with great success (entry 9). Full conversion of β-bromostyrene was observed with four equivalents of Me_2Zn and the product from substitution at the α-position was isolated in 71 % yield after a crude aqueous workup. Due to the limited time at hand no other amines have been tested in the reaction so far, but the experiments are ongoing and other saturated cyclic amines are expected to perform equally well.

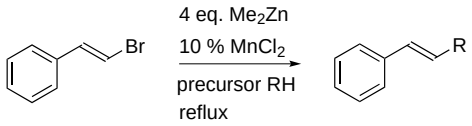
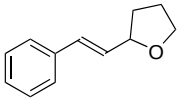
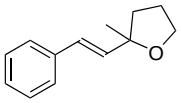
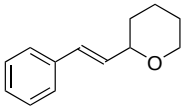
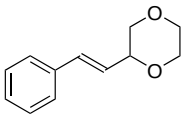
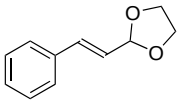
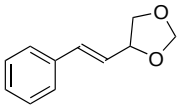
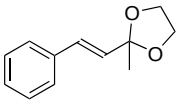
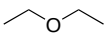
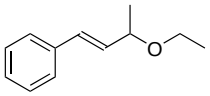
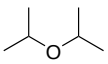
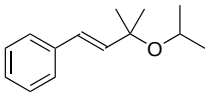
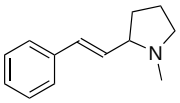
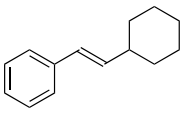
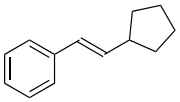


Table 4.3: Expanding the scope of the reaction to include a variety of radical precursors in the reaction with β-bromostyrene. The precursor is used as the solvent and the reaction temperature is the reflux temperature of that particular solvent. The yields specified in the table are the isolated yields of the pure product.

Entry	Precursor	Conv.[a] (%)	Product	Yield (%)
1		85		47
2[b]		100		65
3		100		40
4		77		44
5		83		31
				16
6[b]		82		34
7		64		67
8		31		12

continues...

Entry	Precursor	Conv.[a] (%)	Product	Yield (%)
9		100		71
10		39		–
11[b]		26		–

[a]Conversion of β-bromostyrene from GC analysis.
[b]Only three equivalents of Me_2Zn used.

Cyclohexane gave 33 % conversion with three equivalents of Me_2Zn and 39 % conversion with four equivalents of Me_2Zn (entry 10). The unreacted starting material and the product could not be separated by chromatography and hence no isolated yields nor spectroscopic data are available for this reaction so far. Cyclopentane gave 26 % with three equivalents of Me_2Zn (entry 11). This reaction has not yet been attempted with a larger amount of Me_2Zn, nor has it been scaled up and attempted isolated, but the same inseparable reaction mixture as for the reaction with cyclohexane is anticipated.

The use of cyclopentanone resulted in no conversion of the β-bromostyrene at all, but instead large quantities of the Aldol condensation product from reaction of a cyclopentanonyl radical with cyclopentanone was observed (not shown in the table). The use of cyclopentyl chloride as precursor gave rise to a myriad of peaks in the GC chromatogram: Almost no β-bromostyrene was left, but large peaks from the formation of 1,1'-bicyclopentyl, 1,1'-bi(cyclopentan)ene and β-chlorostyrene were observed (not shown in the table). The use of propionaldehyde as the precursor also resulted in the formation of many different compounds (not shown in the table).

From these experiments it must be concluded that for the reaction to work well the scope of radical precursors is limited to cyclic ethers, diethyl ether and N-methylpyrrolidine, possibly also other saturated cyclic amines. Other acyclic ethers and cycloalkanes may be used, but the yields are very low, and no functional groups may be present on the cycloalkanes which can be abstracted by a radical initiator (halogens) or react with a nucleophilic radical (electrophiles). Care should be taken to employ only radical precursors with no peroxides present as they presumably retard or even completely quench the reaction.

4.3.3 Substituted β-bromostyrenes

A range of substituted β-bromostyrenes as well as 2-(2-bromovinyl)naphthalene and 2-bromoindene were tested as substrates under the standard reaction conditions. The general reaction and the results are shown in table 4.4. The substituted β-bromostyrenes were synthesized following a published procedure for a $Mn(OAc)_2$ catalyzed Hunsdiecker-type reaction.[197]

p-Fluoro-, *p*-chloro-, *p*-bromo- and *o*-chloro-β-bromostyrene could be used as substrates employing the standard reaction conditions and the products were easily isolated as the pure compounds in yields that were better than for the unsubstituted β-bromostyrene (entries 1–4). This could be due to the slightly electron withdrawing effect of the substituents, which may activate the double bond for attack of a nucleophilic radical, if that is indeed the mechanism. If this is the case then substrates with highly electron withdrawing substituents in the para position should perform even better under the applied reaction conditions. Unfortunately the only compound available of this type was *p*-nitro-β-bromostyrene (not shown in the table), which after being subjected to the standard reaction conditions showed neither starting material nor product by GC/MS analysis.

The use of electron donating substituents did not alter the outcome of the reaction to any notable extent. *p*-Methyl-, *p*-hydroxy- and *p*-methoxy-β-bromostyrene (entries 5–7) resulted in 39, 39 and 37 % isolated yield respectively, which is very similar to the yield obtained with the unsubstituted β-bromostyrene, and the use of 3,4-methylendioxy-β-bromostyrene (entry 8) as a substrate gave an isolated yield of 54 %, which is higher than for the unsubstituted substrate.

Other substrates 2-(2-Bromovinyl)naphthalene (entry 9) reacted reluctantly. After refluxing for one night under the standard reaction conditions a large peak from the starting material was still observed by GC/MS. An additional 10 % of $MnCl_2$ and three equivalents of Me_2Zn were added and the reaction mixture refluxed for another 24 hours. Despite the extra reagents and the prolonged reaction time the isolated yield was a mere 21 %. From the GC spectrum several peaks could be observed, apart from the starting material and the desired product. Most notable of these was the occurrence of a peak with a m/z of 302, which contains one bromine, and a peak with a m/z of 312, which contains two bromines. The first corresponds to the exchange of a hydrogen for a tetrahydrofuranyl substituent somewhere in the starting material; the latter corresponds to the exchange of a hydrogen for a bromine.

The reaction between 2-Bromoindene and THF (entry 10) seems to be quite selective but is very slow. With 10 % of $MnCl_2$ and three equivalents of Me_2Zn

the ratio between product and starting material was very low after refluxing for two days. An additional 10 % of $MnCl_2$ and three equivalents of Me_2Zn were added and the reaction mixture refluxed for another 24 hours. This increased the ratio to approximately the double; the isolated yield was 18 %. No byproducts were observed in any large amounts, and the starting material was recovered in 28 %.

An attempt was made to employ α-methyl-β-bromostyrene as a substrate (not shown in the table), but the reaction required the addition of four times the regular amounts of $MnCl_2$ and Me_2Zn for a reasonable consumption of starting material to be achieved. Even then the reaction was very slow and furthermore resulted in a mixture of compounds from which the desired product could not be isolated.

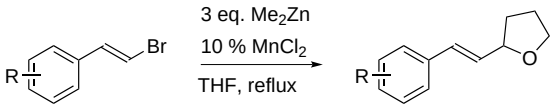
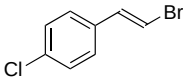
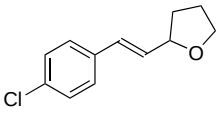
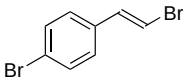
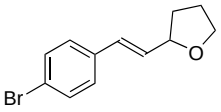
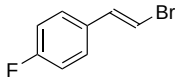
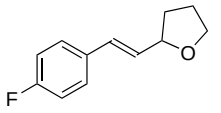
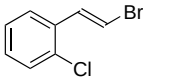
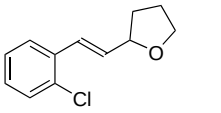
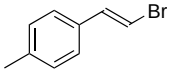
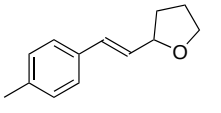
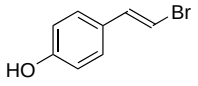
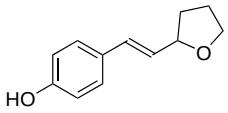
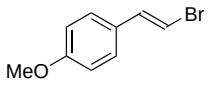
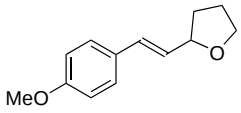
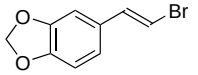
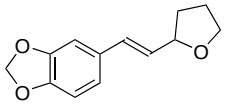
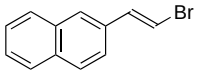
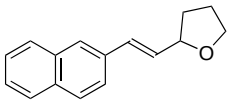
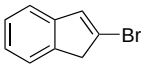
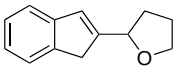


Table 4.4: Applying substituted β-bromostyrenes as substrates in the reaction with THF. The yields specified in the table are the isolated yields of the pure product.

Entry	Substrate	Product	Yield (%)
1			48
2			48
3			40
4[a]			54
5			39

continues. . .

Entry	Substrate	Products	Yield (%)
6[a]			39
7[a]			37
8[a]			54
9[b]			21
10[b]			18

[a]Prolonged reaction time; see experimental section for details.
[b]Twice the amount of reagents used; see experimental section for details.

4.4 Reaction mechanism

Evidence for a radical reaction Initially, the reaction was believed to be a radical reaction, initiated by triplet oxygen or by $MnCl_2$ when present. This hypothesis was substantiated by several experiments. Firstly, running the reaction in the presence of stoichiometric amounts of TEMPO resulted in complete quenching of the reaction with no formation of a product observed. This strongly indicates that the reaction is indeed running by a radical mechanism. Addition of substoichiometric amounts of TEMPO does give some quenching of the reaction but not completely, indicating that the reaction is not a chain reaction. This finding is also supported by the fact that the conversion and the yield increased with increasing amounts of Me_2Zn.

When the reaction was run under completely air free conditions and with no $MnCl_2$ present, no formation of product was observed. This also points towards a radical mechanism, initiated by the diradical triplet oxygen. When the reaction is run under air free conditions but with 10 % of $MnCl_2$ present the reaction gives 43 % conversion and 27 % formation of product, which shows that the reaction can be initiated by $MnCl_2$ alone, but apparently runs better with a combination of oxygen and $MnCl_2$. Increasing the amount of $MnCl_2$

to 100 %, still under completely air-free conditions, did not improve the yield compared to the reaction with a 10 % loading.

The role of Me_2Zn Several plausible mechanisms can be proposed with inspiration from the literature presented in the introduction. Me_2Zn is known to react with triplet oxygen and form methyl radicals, which are highly reactive species.[142] This is most likely the mechanism when the reaction is running in the absence of $MnCl_2$. The methyl radical would react with THF, forming a tetrahydrofuran-2-yl radical, which would either abstract a hydrogen from THF, forming a new tetrahydrofuran-2-yl radical or react with a β-bromostyrene molecule. Nucleophilic radical addition to β-bromostyrene would preferentially occur in the β-position, as this would result in the formation of a benzylic radical, which is relatively stable due to resonance. The formed benzylic radical would then eliminate a bromo radical and form the product. This mechanism is shown in figure 4.19.

The mere formation of a tetrahydrofuran-2-yl radical is not enough to make the reaction run, as was shown from the attempts to initiate the reaction with benzoyl peroxide. Since the reaction occurs in the presence of a zinc reagent, but not with another radical initiator, it is natural to assume that some zinc-activation of the substrate occurs, as is also suggested by Bertrand and coworkers.[142] If this is the case then the formation of an organozinc intermediate prior to the final elimination may also be plausible, similar to the organozinc intermediate for the addition of a tetrahydrofuran-2-yl radical to an acetylene proposed by Chen and Guo.[144] This would also explain the high selectivity for the formation of the (*E*)-isomer observed. This mechanism is shown at the bottom of figure 4.19.

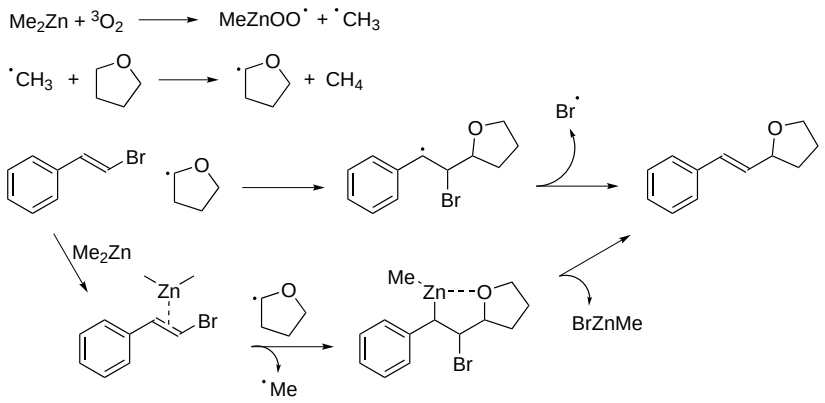


Figure 4.19: The anticipated reaction pathway for the formation of (*E*)-2-styryltetrahydrofuran in the absence of $MnCl_2$.

Chen and Guo substantiate their claim about the existence of an organozinc intermediate by quenching the reaction with iodine, thus trapping the α-zinc species as an α-iodo compound. A similar experiment was performed in the hope of trapping such an intermediate, but no such species was detected by GC/MS. The absence of an iodo-compound may be explained by a number of reasons, and does not necessarily disprove the existence of the aforementioned organozinc intermediate. For one the β-bromo-α-iodo-compound may not be detected by GC/MS as it is simply too heavy.

Another explanation would be the lifetime of the organozinc intermediate: Maybe it is indeed formed, but eliminates more easily to form the product than what is the case in the example by Chen and Guo, where the intermediate does not break down until the reaction is quenched. The paramount difference between these two reactions is that one is an addition, which needs to abstract or combine with a radical to terminate, whereas the other is an addition-elimination. This also means that there is no point in quenching the reaction with deuterated water, as was also done by Chen and Guo, because the quenching in the addition-elimination reaction only destroys excess reagent and does not conclude the reaction itself, as is the case with the addition reaction.

A third explanation of course could be that the organozinc intermediate does not exist at all, and that the preference for formation of the (*E*)-isomer is simply due to the fact that this product is more stable, and that the benzylic radical intermediate is long-lived enough to eliminate only from the conformer that yields the more stable product.

In favor of the existence of some kind of coordination of zinc to the double bond of the substrate is the fact, that when a methyl substituent was present on the α-carbon of the β-bromostyrene the reaction was greatly retarded, which could be explained by the steric bulk of the methyl group hindering efficient coordination to the zinc, thus leading to the formation of a myriad of byproducts, which are otherwise not observed.

The role of $MnCl_2$ When $MnCl_2$ is added to the reaction mixture the yield is increased significantly, regardless of which radical initiator is employed, although the reaction does not run when using only $MnCl_2$ in the absence of a radical initiator. This could indicate a manganese catalyzed activation of the substrate, which apparently is more efficient than what occurs with the zinc regent alone. In addition hereto manganese must also play a role in the initiation of the radical process, as no radical reaction occurs under completely air-free conditions in the absence of $MnCl_2$, but does occur under air-free conditions in the presence of $MnCl_2$. It is quite probable that the reaction runs by another mechanism with $MnCl_2$ present, or that two different mechanisms resulting in

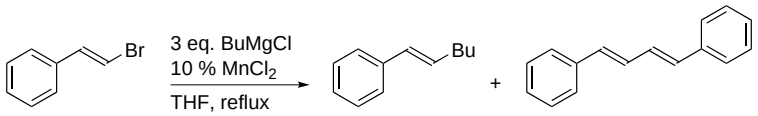


Figure 4.20: Reacting β-bromostyrene with BuMgCl in the presence of 10 % $MnCl_2$ in refluxing THF results in the formation of hex-1-en-1-ylbenzene.

the same product run simultaneously.

In the radical cyclization reaction presented by Oshima and coworkers the active catalytic species is a tributylmanganate species from the reaction of $MnCl_2$ with three equivalents of butyllithium or butylmagnesium bromide.[159] They also report the necessity of having oxygen present when the reaction is run with only catalytic amounts of $MnCl_2$, otherwise the reaction does not run to completion, which also corresponds well to what was observed in the experiments under completely air-free conditions. A similar mechanism might be in play here, involving a trimethylmanganate species which may abstract a bromo radical from β-bromostyrene or a hydrogen from THF, or both. Continuous formation of the active manganate by oxidation of the resulting manganese complex with air and subsequent reaction with fresh Me_2Zn in some fashion makes the reaction catalytic in $MnCl_2$, but dependent on stoichiometric amounts of Me_2Zn and the presence of air for an optimal yield.

If the active species is indeed a trimethylmanganate species, the reaction should also work with a tributylmanganate species as in the example by Oshima. This seems not to be the case: Applying the reaction conditions specified by Oshima and employing three equivalents of BuMgCl together with 10 % of $MnCl_2$ does result in the complete consumption of β-bromostyrene, but does not result in the formation of 2-styryltetrahydrofuran. Instead the major products observed by GC/MS are hex-1-en-1-ylbenzene from the addition-elimination of a butyl radical and 1,4-diphenylbuta-1,3-diene from what appears to be a sort of Ullmann coupling between two molecules of β-bromostyrene. The reaction is shown in figure 4.20.

Lewis acid activation? As mentioned previously the zinc and possibly also the manganese may act as a Lewis acid, activating the double bond towards attack by a nucleophilic radical species. Contrary to what would be expected based on this hypothesis, performing the reaction in the presence of a well known Lewis acid like $BF_3{\cdot}Et_2O$ did not increase the yield; instead it more or less quenched the reaction. The addition of other Lewis acids, like the $FeCl_3$ tested in table 4.2, did not improve the yield either; rather it decreased the yield, although it did not directly quench the reaction.

4.5 Summary and conclusions

The initial goal of the work described in this chapter was the development of new manganese catalyzed cross coupling reactions. This was not achieved, but a lot of crucial preliminary experiments have been performed which may serve as a guidance to other scientists engaging in a similar cause. Even negative results can be useful, in the sense of preventing one from repeating unfruitful experiments and thus wasting precious time. As was described in section 4.2.4 valuable information has been obtained and a course has been given along which it would be feasible to take the project in future experiments.

On the other hand this search for manganese catalyzed cross coupling reactions led to the serendipitous discovery of a new radical reaction. The reaction was assessed interesting enough to spend some time optimizing the reaction conditions and exploring the scope and limitations of the method.

It was found that the reaction gave the best yield when adding three to four equivalents of dimethyl zinc to a solution of β-bromostyrene in THF in the presence of 10 % of $MnCl_2$, $Mn(OAc)_3$ or $CoCl_2$ and subsequently heating the reaction mixture to reflux under vigorous stirring over night. This afforded 2-styryltetrahydrofuran in more than 70 % yield by GC/MS, although the isolated yield was only 47 %. The same reaction conditions could be applied to the reaction of β-bromostyrene with a range of cyclic ethers resulting in similar yields, as well as with some acyclic ethers and cycloalkanes with considerably diminished yields. *N*-Methylpyrrolidine performed excellently as radical precursor, giving the corresponding α-functionalized amine in 71 % isolated yield. Other saturated cyclic amines are expected to perform equally well and the experimental work is ongoing with the aim of including this compound class to the substrate scope of the reaction.

A variety of electron-donating substituents were tolerated on the aromatic ring of β-bromostyrene in its reaction with THF without affecting the yield remarkably, and halogen substituents even improved the yield slightly. Unfortunately the only β-bromostyrene with a strongly electron withdrawing substituent available for testing was *p*-nitro-β-bromostyrene, which presumably decomposed under the reaction conditions. The presence of a methyl-substituent in the α-position retarded the reaction to such an extent that four times the usual amount of reagents as well as four times the usual reaction time was necessary in order to reach a reasonable level of conversion and still the outcome was an inseparable mixture of compounds.

The method in itself is a useful new way of synthesizing substituted styryl derivatives from bromostyrenes and reactants like THF which are normally inert under for example Heck or Kumada reaction conditions. It deviates from more classic radical reaction conditions by not employing tin reagents, a feature of

the reaction which is obviously attractive due to the severe toxicity of tin. What is possibly more important than the development of a new synthetic method is the information that it provides regarding the use of manganese and dimethyl zinc in radical reactions.

4.6 Experimental part

All solvents used were of HPLC grade, all chemicals were bought from Sigma Aldrich, unless otherwise stated. For dry column vacuum chromatography (DCVC)[67] was used Merck Silica Gel 60, 0.015-0.040 mm. Reactions were monitored by GCMS on a Shimadzu GCMS-QP5000 instrument. NMR spectra were recorded on a Bruker 400 MHz instrument. Chemical shifts were measured relative to the signals of residual $CHCl_3$ (δ_H 7.26 ppm, δ_C 77.16 ppm)[69] and are reported in ppm from lowest to highest field. Mass Spectrometry was performed on a Shimadzu GCMS-QP5000 instrument and are given as data sets consisting of mass and relative intensity (in parentheses). HRMS data was obtained by ultra high performance liquid chromatography high resolution mass spectrometry (UHPLC-HRMS) on a maXis G3 quadrupole time of flight mass spectrometer (Bruker Daltronics, Bremen) equipped with an electrospray (ESI) source.

General procedure for the $MnCl_2$ enhanced radical formation of styryl derivatives

In a 50 ml roundbottomed flask equipped with a magnetic stirbar and a condenser was placed $MnCl_2$ (12.6 mg; 0.1 mmol; 10 %), β-bromostyrene (130 μl; 183 mg; 1.0 mmol) and 25 ml of the dry radical precursor as solvent. Three or four equivalents of Me_2Zn (1.0 M in heptanes; 3–4 ml; 3–4 mmol; or 2.0 M in toluene; 1.5–2 ml; 3–4 mmol) was added and the reaction heated to reflux for 20 hours.

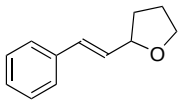
The reaction was quenched with 1.0 M HCl (10 ml) and stirred until both phases were clear. The phases were separated and the aqueous phase extracted with diethyl ether (2 x 20 ml) and discarded. The combined organic phases were washed with water (20 ml), dried over $MgSO_4$, filtered through a fluted filter paper and concentrated in vacuo to give the crude product, which could be further purified by chromatography.

General procedure for the synthesis of substituted β-bromostyrenes

The employed substituted β-bromostyrenes were synthesized from the corresponding cinnamic acids, loosely following a published procedure for a $Mn(OAc)_2$ catalyzed Hunsdiecker reaction.[197]

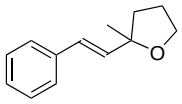
In a 100 ml roundbottomed flask was placed the cinnamic acid (15 mmol), NBS (2.67 g; 15 mmol), $Mn(OAc)_2$ (0.26 g; 1.5 mmol; 10 %) and 50 ml of a 1:1 mixture of water and acetonitrile. The reaction mixture was stirred in the open flask at room temperature overnight. The crude reaction mixture was extracted with DCM and the organic phase concentrated in vacuo. The residue was purified by flash chromatography to yield the pure product.

(*E*)-2-Styryltetrahydrofuran



Prepared from β-bromostyrene and THF. Four equivalents of Me_2Zn used. Purified by DCVC, eluting from heptane to ethyl acetate, 1 % increments, to yield the product as a colorless oil in 47 % yield. (GC yield: 79 %). ^{1}H-NMR(400 MHz, $CDCl_3$) δ 7.38 (d, J = 7.2 Hz, 2H), 7.30 (t, J = 7.5 Hz, 2H), 7.22 (t, J = 7.3 Hz, 1H), 6.59 (d, J = 15.8 Hz, 1H), 6.21 (dd, J = 15.8, 6.6 Hz, 1H), 4.47 (td, J = 7.5, 1.0 Hz, 1H), 3.97 (dd, J = 14.2, 7.7 Hz, 1H), 3.84 (td, J = 7.9, 6.2 Hz, 1H), 2.19–2.05 (m, 1H), 2.04–1.85 (m, 2H), 1.77–1.64 (m, 1H). ^{13}C-NMR(101 MHz, $CDCl_3$) δ 136.9, 130.6, 130.5, 128.6, 127.5, 126.5, 79.7, 68.2, 32.5, 26.0. MS: m/z 174 (94) [M^+], 146 (14), 131 (72), 129 (25), 115 (33), 104 (70), 42 (100). The observed chemical shifts are in accordance with the literature values.[198]

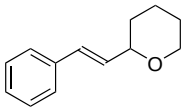
(*E*)-2-Methyl-2-styryltetrahydrofuran



Prepared from β-bromostyrene and 2-methyltetrahydrofuran. Three equivalents of Me_2Zn used. Refluxed for two days. Purified by DCVC, eluting from heptane to ethyl acetate, 1 % increments, to yield the product as a colorless oil in 65 % yield. ^{1}H-NMR(400 MHz, $CDCl_3$) δ 7.40 (d, J = 7.2 Hz, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.22 (t, J = 7.3 Hz, 1H), 6.57 (d, J = 16.0 Hz, 1H), 6.26 (d, J = 16.0 Hz, 1H), 3.96 (t, J = 6.8 Hz, 2H), 2.04–1.90 (m, 3H), 1.85–1.76 (m, 1H),

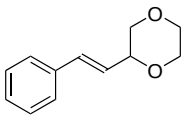
1.43 (s, 3H). ^{13}C-NMR(101 MHz, $CDCl_3$) δ 137.2, 135.5, 128.5, 127.2, 126.8, 126.4, 82.4, 67.7, 37.9, 26.8, 25.8. MS: m/z 188 (27) [M^+], 173 (100), 131 (71), 103 (33). HRMS calcd. for $C_{13}H_{17}O$ [MH^+]: 189.1279, found: 189.1290.

(*E*)-2-Styryltetrahydropyran



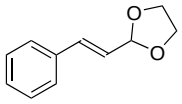
Prepared from β-bromostyrene and THP. Four equivalents of Me_2Zn used. Purified by DCVC, eluting from heptane to ethyl acetate, 1 % increments, to yield the product as a colorless oil in 40 % yield. ^{1}H-NMR(400 MHz, $CDCl_3$) δ 7.39 (d, J = 7.2 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.23 (t, J = 7.3 Hz, 1H), 6.60 (d, J = 16.1 Hz, 1H), 6.23 (dd, J = 16.1, 5.8 Hz, 1H), 4.12–4.05 (m, 1H), 4.02–3.95 (m, 1H), 3.60–3.52 (m, 1H), 1.94–1.86 (m, 1H), 1.79–1.72 (m, 1H), 1.66–1.48 (m, 2H). ^{13}C-NMR(101 MHz, $CDCl_3$) δ 137.1, 131.0, 129.8, 128.6, 127.5, 126.5, 78.1, 68.5, 32.4, 26.0, 23.6. MS: m/z 188 (73) [M^+], 187 (17), 131 (68), 115 (25), 104 (100), 91 (35), 77 (24), 55 (69). The observed chemical shifts are in accordance with the literature values.[199]

(*E*)-2-Styryl-1,4-dioxane



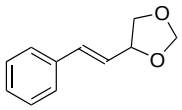
Prepared from β-bromostyrene and 1,4-dioxan. Four equivalents of Me_2Zn used. Purified by DCVC, eluting from heptane to ethyl acetate, 1 % increments, to yield the product as a colorless oil in 44 % yield. ^{1}H-NMR(400 MHz, $CDCl_3$) δ 7.37 (d, J = 7.2 Hz, 1H), 7.30 (t, J = 7.4 Hz, 1H), 7.24 (d, J = 7.2 Hz, 1H), 6.68 (d, J = 16.0 Hz, 1H), 6.08 (dd, J = 16.0, 6.2 Hz, 1H), 4.29–4.21 (m, 1H), 3.90–3.60 (m, 5H), 3.46–3.36 (m, 1H). ^{13}C-NMR(101 MHz, $CDCl_3$) δ 136.3, 132.6, 128.5, 127.8, 126.4, 125.0, 76.0, 70.8, 66.5, 66.2. MS: m/z 190 (15) [M^+], 131 (66), 104 (23), 86 (100). The observed chemical shifts are in accordance with the literature values.[200]

(*E*)-2-Styryl-1,3-dioxolane



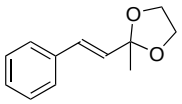
Prepared from β-bromostyrene and 1,3-dioxolan. Four equivalents of Me_2Zn used. The reaction was worked up with 1.0 M NaOH instead of HCl to avoid formation of cinnemaldehyde. Purified by DCVC, eluting from heptane to ethyl acetate, 1 % increments, to yield the product as a colorless oil in 31 % yield. ^{1}H-NMR(400 MHz, $CDCl_3$) δ 7.43 (d, J = 7.0 Hz, 2H), 7.34 (t, J = 7.2 Hz, 2H), 7.30–7.25 (m, 1H), 6.79 (d, J = 16.0 Hz, 1H), 6.18 (dd, J = 16.0, 6.0 Hz, 1H), 5.44 (d, J = 6.0 Hz, 1H), 4.10–4.02 (m, 2H), 4.01–3.92 (m, 2H). ^{13}C-NMR(101 MHz, $CDCl_3$) δ 135.9, 135.0, 128.7, 128.5, 127.1, 125.2, 104.0, 65.2. MS: m/z 176 (34) [M^+], 131 (31), 115 (43), 104 (100), 77 (25). The observed chemical shifts are in accordance with the literature values.[198]

(*E*)-4-Styryl-1,3-dioxolane



Prepared from β-bromostyrene and 1,3-dioxolan. Four equivalents of Me_2Zn used. Refluxed for two days. Purified by DCVC, eluting from heptane to ethyl acetate, 2 % increments, to yield the product as a colorless oil in 16 % yield. ^{1}H-NMR(400 MHz, $CDCl_3$) δ 7.33–7.29 (m, 2H), 7.27–7.22 (m, 2H), 7.21–7.15 (m, 1H), 6.60 (d, J = 15.0 Hz, 1H), 6.10 (dd, J = 15.0, 7.5 Hz, 1H), 5.05 (s, 1H), 4.92 (s, 1H), 4.53 (q, J = 7.5 Hz, 1H), 4.03 (dd, J = 8.0, 6.7 Hz, 1H), 3.55 (dd, J = 8.0, 6.7 Hz, 1H). ^{13}C-NMR(101 MHz, $CDCl_3$) δ 136.2, 133.5, 128.2, 126.7, 126.3, 95.6, 77.0, 69.9. MS: m/z 176 (30) [M^+], 145 (28), 131 (69), 118 (69), 115 (100), 104 (59). Sample submitted for HRMS.

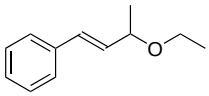
(*E*)-2-Methyl-2-styryl-1,3-dioxolane



Prepared from β-bromostyrene and 2-methyl-1,3-dioxolan. Three equivalents of Me_2Zn used. The reaction was worked up with 1.0 M NaOH instead of HCl to avoid formation of 4-phenylbut-3-en-2-one. Purified by DCVC, eluting from heptane to ethyl acetate, 1 % increments, to yield the product as a colorless oil in 34 % yield. ^{1}H-NMR(400 MHz, $CDCl_3$) δ 7.40–7.35 (m, 2H), 7.34–7.26 (m,

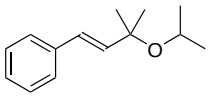
2H), 7.26–7.19 (m, 1H), 6.69 (d, J = 16.0 Hz, 1H), 6.14 (d, J = 16.0 Hz, 1H), 4.02–3.89 (m, 4H), 1.55 (s, 1H). ^{13}C-NMR(101 MHz, $CDCl_3$) δ 136.3, 129.9, 129.8, 128.7, 128.0, 126.8, 107.7, 64.7, 25.3. MS: m/z 190 (7) [M^+], 175 (100), 131 (60), 103 (32), 87 (21), 77 (20), 43 (56). The observed chemical shifts are in accordance with the literature values.[201]

(*E*)-(3-Ethoxybut-1-en-1-yl)benzene



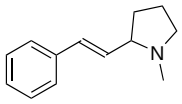
Prepared from β-bromostyrene and diethyl ether. Four equivalents of Me_2Zn used. Refluxed for two days. Purified by DCVC, eluting from heptane to ethyl acetate, 1 % increments, to yield the product as a pale yellow oil in 67 % yield. ^{1}H-NMR(400 MHz, $CDCl_3$) δ 7.38 (d, J = 7.3 Hz, 2H), 7.30 (t, J = 7.5 Hz, 2H), 7.22 (t, J = 7.3 Hz, 1H), 6.51 (d, J = 15.9 Hz, 1H), 6.12 (dd, J = 15.9, 7.5 Hz, 1H), 3.99 (p, J = 6.7 Hz, 1H), 3.63–3.50 (m, 1H), 3.46–3.35 (m, 1H), 1.34 (d, J = 6.4 Hz, 3H), 1.21 (t, J = 7.0 Hz, 3H). ^{13}C-NMR(101 MHz, $CDCl_3$) δ 136.8, 132.2, 130.8, 128.6, 127.6, 126.5, 76.4, 63.6, 21.8, 15.5. MS: m/z 176 (16) [M^+], 161 (15), 147 (12), 131 (17), 115 (17), 105 (12), 91 (23), 43 (100). The observed chemical shifts are in accordance with the literature values.[202]

(*E*)-(3-Isopropoxy-3-methylbut-1-en-1-yl)benzene



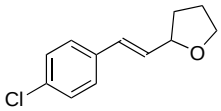
Prepared from β-bromostyrene and diisopropyl ether. Four equivalents of Me_2Zn used. Refluxed for two days. Purified by DCVC, eluting from heptane to ethyl acetate, 1 % increments, to yield the product as a colorless oil in 12 % yield. ^{1}H-NMR(400 MHz, $CDCl_3$) δ 7.32 (d, J = 7.3 Hz, 2H), 7.25 (t, J = 7.6 Hz, 2H), 7.19–7.13 (m, 1H), 6.39 (d, J = 16.4 Hz, 1H), 6.19 (d, J = 16.4 Hz, 1H), 3.65 (hept, J = 6.2 Hz, 1H), 1.30 (s, 6H), 1.05 (d, J = 6.2 Hz, 6H). ^{13}C-NMR(101 MHz, $CDCl_3$) δ 137.2, 136.6, 128.7, 128.4, 127.6, 126.5, 75.4, 65.0, 32.0, 27.2, 25.2. MS: m/z 204 (6) [M^+], 189 (8), 162 (21), 147 (99), 145 (42), 129 (35), 91 (36), 43 (100). Sample submitted for HRMS.

(*E*)-1-methyl-2-styrylpyrrolidine



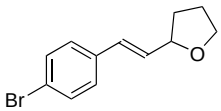
Prepared from β-bromostyrene and *N*-methylpyrrolidine. Four equivalents of Me_2Zn used. Refluxed for two days. Aqueous workup yielded the product as a yellow oil in 71 % yield. ^{1}H-NMR(400 MHz, $CDCl_3$) δ 7.42–7.37 (m, 2H), 7.34–7.28 (m, 2H), 7.25–7.19 (m, 1H), 6.51 (d, J = 15.8 Hz, 1H), 6.12 (dd, J = 15.8, 8.4 Hz, 1H), 3.19–3.12 (m, 1H), 2.67 (dd, J = 16.2, 8.3 Hz, 1H), 2.31 (s, 3H), 2.24–2.20 (m, 1H), 2.06–1.99 (m, 1H), 1.95–1.85 (m, 1H), 1.81–1.70 (m, 2H). ^{13}C-NMR(101 MHz, $CDCl_3$) δ 137.0, 132.1, 131.6, 128.5, 127.3, 126.2, 69.6, 56.7, 40.3, 32.2, 22.3. MS: m/z 187 (87) [M^+], 186 (82), 158 (58), 110 (57), 96 (100), 84 (98), 82 (55), 42 (78). Sample submitted for HRMS.

(*E*)-2-(4-Chlorostyryl)tetrahydrofuran



Prepared from (*E*)-1-(2-bromovinyl)-4-chlorobenzene and THF. Three equivalents of Me_2Zn used. Purified by DCVC, eluting from heptane to ethyl acetate, 2 % increments, to yield the product as colorless crystals in 48 % yield. ^{1}H-NMR(400 MHz, $CDCl_3$) δ 7.33–7.24 (m, 4H), 6.54 (d, J = 15.9 Hz, 1H), 6.19 (dd, J = 15.9, 6.5 Hz, 1H), 4.50–4.42 (m, 1H), 4.01–3.92 (m, 1H), 3.89–3.80 (m, 1H), 2.18–2.07 (m, 1H), 2.04–1.88 (m, 2H), 1.76–1.64 (m, 1H). ^{13}C-NMR(101 MHz, $CDCl_3$) δ 135.4, 133.1, 131.3, 129.2, 128.7, 127.7, 79.5, 68.3, 32.4, 26.0. MS: m/z 208 (25) [M^+], 173 (61), 138 (30), 131 (32), 70 (35), 42 (100). The observed chemical shifts are in accordance with the literature values.[145]

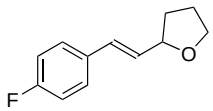
(*E*)-2-(4-Bromostyryl)tetrahydrofuran



Prepared from (*E*)-1-bromo-4-(2-bromovinyl)benzene and THF. Three equivalents of Me_2Zn used. Purified by DCVC, eluting from heptane to ethyl acetate, 1 % increments, to yield the product as colorless crystals in 47 % yield. ^{1}H-NMR(400 MHz, $CDCl_3$) δ 7.45–7.39 (m, 2H), 7.26–7.20 (m, 2H), 6.52 (d, J = 15.8 Hz, 1H), 6.20 (dd, J = 15.8, 6.5 Hz, 1H), 4.49–4.41 (m, 1H), 4.02–3.91

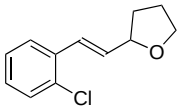
(m, 1H), 3.88–3.79 (m, 1H), 2.18–2.07 (m, 1H), 2.04–1.88 (m, 2H), 1.76–1.64 (m, 1H). ^{13}C-NMR(101 MHz, $CDCl_3$) δ 135.9, 131.7, 131.5, 129.3, 128.1, 121.3, 79.6, 68.3, 32.4, 26.0. MS: m/z 254 (21), 252 (20) [M^+], 173 (79), 131 (45), 128 (25), 115 (24), 103 (29), 102 (31), 70 (35), 42 (100). The observed chemical shifts are in accordance with the literature values.[198]

(*E*)-2-(4-Fluorostyryl)tetrahydrofuran



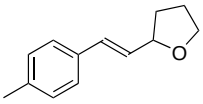
Prepared from (*E*)-1-(2-bromovinyl)-4-fluorobenzene and THF. Three equivalents of Me_2Zn used. Purified by DCVC, eluting from heptane to ethyl acetate, 1 % increments, to yield the product as a colorless oil in 40 % yield. ^{1}H-NMR(400 MHz, $CDCl_3$) δ 7.33 (dd, J = 8.7, 5.4 Hz, 2H), 6.98 (t, J = 8.7 Hz, 2H), 6.54 (d, J = 15.8 Hz, 1H), 6.12 (dd, J = 15.8, 6.6 Hz, 1H), 4.45 (q, J = 6.7 Hz, 1H), 3.96 (q, J = 7.5 Hz, 1H), 3.83 (q, J = 7.9 Hz, 1H), 2.17–2.06 (m, 1H), 2.04–1.87 (m, 2H), 1.75–1.64 (m, 1H). ^{13}C-NMR(101 MHz, $CDCl_3$) δ 162.3 (d, J = 246.5 Hz), 133.1 (d, J = 3.3 Hz), 130.4 (d, J = 2.2 Hz), 129.3, 128.0 (d, J = 8.0 Hz), 115.5 (d, J = 21.6 Hz), 79.6, 68.2, 32.5, 26.0. MS: m/z 192 (55) [M^+], 149 (47), 133 (20), 122 (43), 109 (25), 70 (38), 42 (100). The observed chemical shifts are in accordance with the literature values.[198]

(*E*)-2-(2-Chlorostyryl)tetrahydrofuran



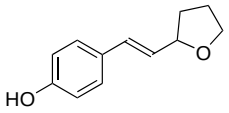
Prepared from (*E*)-1-(2-bromovinyl)-2-chlorobenzene and THF. Three equivalents of Me_2Zn used. Refluxed for three days. Purified by DCVC, eluting from heptane to ethyl acetate, 1 % increments, to yield the product as a colorless oil in 54 % yield. ^{1}H-NMR(400 MHz, $CDCl_3$) δ 7.53 (dd, J = 7.6, 1.8 Hz, 1H), 7.33 (dd, J = 7.8, 1.5 Hz, 1H), 7.24–7.10 (m, 2H), 6.98 (d, J = 15.8 Hz, 1H), 6.20 (dd, J = 15.8, 6.5 Hz, 1H), 4.51 (q, J = 6.9 Hz, 1H), 3.97 (dd, J = 14.4, 7.5 Hz, 1H), 3.84 (td, J = 7.9, 6.3 Hz, 1H), 2.19–2.08 (m, 1H), 2.04–1.87 (m, 2H), 1.77–1.66 (m, 1H). ^{13}C-NMR(101 MHz, $CDCl_3$) δ 135.0, 133.5, 133.1, 129.7, 128.5, 126.9, 126.8, 126.6, 79.5, 68.2, 32.4, 25.9. MS: m/z 208 (43) [M^+], 173 (72), 145 (22), 138 (36), 131 (59). HRMS calcd. for $C_{12}H_{14}ClO$ [MH^+]: 209.0733, found: 209.0731.

(*E*)-2-(4-Methylstyryl)tetrahydrofuran



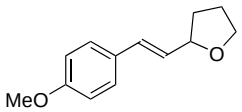
Prepared from (*E*)-1-(2-bromovinyl)-4-methylbenzene and THF. Three equivalents of Me_2Zn used. Purified by DCVC, eluting from heptane to ethyl acetate, 1 % increments, to yield the product as a colorless oil in 39 % yield. ^{1}H-NMR(400 MHz, $CDCl_3$) δ 7.29 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 6.56 (d, J = 15.8 Hz, 1H), 6.17 (dd, J = 15.8, 6.7 Hz, 1H), 4.47 (q, J = 7.0 Hz, 1H), 3.98 (dd, J = 14.3, 7.5 Hz, 1H), 3.84 (td, J = 7.9, 6.2 Hz, 1H), 2.34 (s, 3H), 2.19–2.07 (m, 1H), 2.06–1.88 (m, 2H), 1.78–1.66 (m, 1H). ^{13}C-NMR(101 MHz, $CDCl_3$) δ 137.4, 134.2, 130.5, 129.6, 129.3, 126.5, 79.9, 68.2, 32.5, 26.0, 21.3. MS: m/z 188 (62) [M^+], 173 (54), 145 (56), 131 (56), 118 (47), 117 (45), 115 (41), 42 (100). The observed chemical shifts are in accordance with the literature values.[198]

(*E*)-4-(2-(Tetrahydrofuran-2-yl)vinyl)phenol



Prepared from (*E*)-4-(2-bromovinyl)phenol and THF. Three equivalents of Me_2Zn used. Refluxed for two days. Purified by DCVC, eluting from heptane to ethyl acetate, 5 % increments, to yield the product as a colorless oil in 39 % yield. ^{1}H-NMR(400 MHz, $CDCl_3$) δ 7.16 (d, J = 8.5 Hz, 2H), 7.10 (s, 1H), 6.75 (d, J = 8.5 Hz, 2H), 6.48 (d, J = 15.8 Hz, 1H), 5.99 (dd, J = 15.8, 7.2 Hz, 1H), 4.49 (q, J = 6.8 Hz, 1H), 3.99 (dd, J = 14.9, 7.1 Hz, 1H), 3.87 (td, J = 7.9, 6.0 Hz, 1H), 2.19–2.07 (m, 1H), 2.05–1.89 (m, 2H), 1.79–1.65 (m, 1H). ^{13}C-NMR(101 MHz, $CDCl_3$) δ 156.0, 131.2, 129.0, 127.9, 127.2, 115.7, 80.5, 68.1, 32.5, 26.0. MS: m/z 190 (57) [M^+], 189 (22), 147 (73), 133 (60), 131 (47), 120 (72), 107 (47), 42 (100). Sample submitted for HRMS.

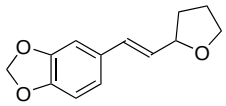
(*E*)-2-(4-Methoxystyryl)tetrahydrofuran



Prepared from (*E*)-1-(2-bromovinyl)-4-methoxybenzene and THF. Three equivalents of Me_2Zn used. Refluxed for two days. Purified by DCVC, eluting from

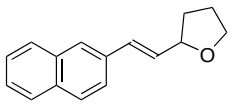
heptane to ethyl acetate, 2 % increments, to yield the product as a colorless oil in 37 % yield. ^{1}H-NMR(400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 6.53 (d, J = 15.8 Hz, 1H), 6.07 (dd, J = 15.8, 6.8 Hz, 1H), 4.44 (q, J = 7.0 Hz, 1H), 3.96 (dd, J = 14.3, 7.6 Hz, 1H), 3.87–3.79 (m, 1H), 3.78 (s, 3H), 2.17–2.05 (m, 1H), 2.05–1.86 (m, 2H), 1.75–1.64 (m, 1H). ^{13}C-NMR(101 MHz, $CDCl_3$) δ 159.2, 130.1, 129.7, 128.3, 127.7, 114.0, 79.9, 68.1, 55.3, 32.5, 26.0. MS: m/z 204 (67) [M^+], 173 (46), 161 (70), 147 (100), 134 (75), 121 (57), 42 (93). The observed chemical shifts are in accordance with the literature values.[198]

(*E*)-5-(2-(Tetrahydrofuran-2-yl)vinyl)benzo[*d*][1,3]dioxole



Prepared from (*E*)-5-(2-bromovinyl)benzo[*d*][1,3]dioxole and THF. Three equivalents of Me_2Zn used. Refluxed for three days. Purified by DCVC, eluting from heptane to ethyl acetate, 2 % increments, to yield the product as a colorless oil in 54 % yield. ^{1}H-NMR(400 MHz, $CDCl_3$) δ 6.91 (d, J = 1.5 Hz, 1H), 6.79 (dd, J = 8.0, 1.5 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 6.48 (d, J = 15.8 Hz, 1H), 6.02 (dd, J = 15.8, 6.7 Hz, 1H), 5.91 (s, 2H), 4.41 (q, J = 7.0 Hz, 1H), 3.94 (dd, J = 14.4, 7.5 Hz, 1H), 3.81 (td, J = 7.9, 6.3 Hz, 1H), 2.15–2.04 (m, 1H), 2.03–1.84 (m, 2H), 1.73–1.61 (m, 1H). ^{13}C-NMR(101 MHz, $CDCl_3$) δ 148.0, 147.2, 131.4, 130.2, 128.8, 121.1, 108.2, 105.8, 101.1, 79.7, 68.1, 32.5, 26.0. MS: m/z 218 (91) [M^+], 175 (32), 161 (25), 148 (63), 135 (52), 131 (42), 42 (100). HRMS calcd. for $C_{13}H_{15}O_3$ [MH^+]: 219.1021, found: 219.1044.

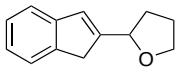
(*E*)-2-(2-(Naphthalen-2-yl)vinyl)tetrahydrofuran



Prepared from (*E*)-2-(2-bromovinyl)naphthalene and THF. After refluxing over night $MnCl_2$ (10 %) and Me_2Zn (3 eq.) was added and the reaction was refluxed for another 16 hours. Purified by DCVC, eluting from heptane to ethyl acetate, 1 % increments, to yield the product as a pale yellow solid in 21 % yield. ^{1}H-NMR(400 MHz, $CDCl_3$) δ 7.73–7.62 (m, 4H), 7.51 (dd, J = 8.6, 1.6 Hz, 1H), 7.39–7.30 (m, 2H), 6.66 (d, J = 15.8 Hz, 1H), 6.25 (dd, J = 15.8, 6.6 Hz, 1H), 4.44 (q, J = 6.9 Hz, 1H), 3.91 (dd, J = 14.4, 7.5 Hz, 1H), 3.78 (td, J = 7.9, 6.3 Hz, 1H), 2.13–2.01 (m, 1H), 1.97–1.82 (m, 2H), 1.72–1.61 (m, 1H). ^{13}C-NMR(101 MHz, $CDCl_3$) δ 134.5, 133.7, 133.1, 131.1, 130.7, 128.2, 128.1,

127.8, 126.5, 126.3, 125.9, 123.8, 79.9, 68.3, 32.6, 26.1. MS: m/z 224 (100) [M^+], 181 (37), 165 (42), 154 (79), 141 (49). The observed chemical shifts are in accordance with the literature values.[145]

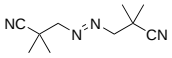
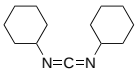
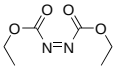
2-(1*H*-Inden-2-yl)tetrahydrofuran



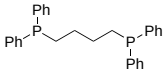
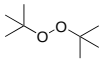
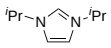
Prepared from 2-bromoindene and THF. After refluxing for three days $MnCl_2$ (10 %) and Me_2Zn (3 eq.) was added and the reaction was refluxed for another 16 hours. Purified by DCVC, eluting from heptane to ethyl acetate, 1 % increments, to yield the product as a colorless oil in 18 % yield. The starting material was recovered in 28 % yield. ^{1}H-NMR(400 MHz, $CDCl_3$) δ 7.43 (dd, J = 7.3, 0.5 Hz, 1H), 7.33 (d, J = 7.4 Hz, 1H), 7.25 (t, J = 7.7 Hz, 1H), 7.15 (td, J = 7.4, 1.2 Hz, 1H), 6.73 (s, 1H), 4.06–3.97 (m, 1H), 3.93–3.84 (m, 1H), 3.41 (d, J = 0.7 Hz, 2H), 2.27–2.15 (m, 1H), 2.06–1.95 (m, 2H), 1.92–1.82 (m, 1H). ^{13}C-NMR(101 MHz, $CDCl_3$) δ 150.6, 144.8, 143.4, 126.8, 126.4, 124.4, 123.8, 120.8, 77.9, 68.3, 38.2, 32.3, 26.1. MS: m/z 186 (48) [M^+], 185 (19), 144 (46), 128 (21), 116 (41), 115 (60), 71 (100). Sample submitted for HRMS.

APPENDIX A

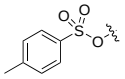
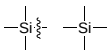
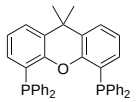
List of Abbreviations

Abbreviation	Full name	Structure
ACN	Acetonitrile	—
AIBN	Azobisisobutyronitrile	
BDE	Bond dissociation energy	—
BTMSA	Bistrimethylsilylacetylene	
COD	1,5-Cyclooctadiene	
d	Doublet	—
DABCO	1,4-Diazabicyclo[2.2.2]octane	
DCC	*N,N'*-dicyclohexylcarbodiimide	
DCM	Dichloromethane	—
DCVC	Dry column vacuum chromatography	—
dd	Doublet of doublets	—
DEAD	Diethyl azodicarboxylate	
DFT	Density functional theory	—
DMAP	4-Dimethylamino pyridine	

continues...

Abbreviation	Full name	Structure
DMF	*N,N*-dimethylformamide	
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone	
DMSO	Dimethyl sulfoxide	
dppb	1,4-Bis(diphenylphosphino)butane	
dt	Doublet of triplets	—
DTBP	Di-*tert*-butyl peroxide	
EI	Electron ionization	—
ESR	Electron spin resonance	—
Et	Ethyl-	—
GC/MS	Gas chromatography / mass spectroscopy	—
hept	septet	—
HRMS	High resolution mass spectroscopy	—
ICP-MS	Inductively coupled plasma mass spectroscopy	—
I^{i}Pr	Di-isopropylimidazolium	
^{i}Pr	*i*-Propyl, *iso*-propyl	—
IR	Infrared	—
KIE	Kinetic isotope effect	—
LDA	Lithium diisopropylamide	
m	Multiplet	—
Me	Methyl-	—
MS	Mass spectrometry	—
n-Bu	Normal (straight chain) butyl-	—
NBS	*N*-bromosuccinimide	
NHC	N-heterocyclic carbene	—
NICS	Nucleus independent chemical shift	—
NMP	*N*-methyl-2-pyrrolidone	

continues...

Abbreviation	Full name	Structure
NMR	Nuclear magnetic resonance	—
p	Quintet	—
PAH	Polyaromatic hydrocarbon	—
PE	Petroleum ether	—
Ph	Phenyl-	—
ppb	Parts per billion	—
ppm	Parts per million	—
q	Quartet	—
r.t.	Room temperature	—
s	Singlet	—
SET	Single electron transfer	—
t	Triplet	—
TBAB	Tetrabutylammoniumbromide	—
TBAF	Tetrabutylammoniumfluoride	—
tBu	*t*-Butyl, *tert*-butyl, tertiary butyl	—
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxy	
TIPS	Triisopropylsilyl	
TIPSA	Triisopropylsilylacetylene	—
THF	Tetrahydrofuran	
THP	Tetrahydropyran	
TLC	Thin layer chromatography	—
TMEDA	*N,N,N',N'*-tetramethylethylenediamine	
TON	Turn-over number	—
Ts	Tosyl; *p*-toluenesulfonyl	
TMS	Trimethylsilyl or tetramethylsilan (NMR)	
TMSA	Trimethylsilylacetylene	—
TMU	1,1,3,3-Tetramethylurea	
xanthphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene	

APPENDIX B

Publications

Dehydrogenative Coupling of Primary Alcohols To Form Esters Catalyzed by a Ruthenium N-Heterocyclic Carbene Complex

Amanda Sølvhøj and Robert Madsen, *Organometallics* **2011**, 30, 6044–6048.

ORGANOMETALLICS

Article

pubs.acs.org/Organometallics

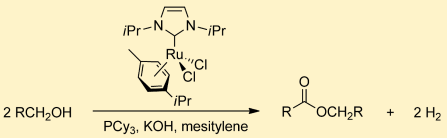
Dehydrogenative Coupling of Primary Alcohols To Form Esters Catalyzed by a Ruthenium N-Heterocyclic Carbene Complex

Amanda Sølvhøj and Robert Madsen*

Department of Chemistry, Technical University of Denmark, DK-2800 Lyngby, Denmark

Supporting Information

ABSTRACT: The ruthenium complex [$RuCl_2$(I*i*Pr)(*p*-cymene)] catalyzes the direct condensation of primary alcohols into esters and lactones with the release of hydrogen gas. The reaction is most effective with linear aliphatic alcohols and 1,4-diols and is believed to proceed with a ruthenium dihydride as the catalytically active species.



INTRODUCTION

The synthesis of an ester is one of the most fundamental transformations in organic chemistry. The reaction is usually performed by coupling of a carboxylic acid or a derivative of a carboxylic acid with an alcohol.[1] Although high yields can be obtained, the need for activation of the acid often leads to the formation of a significant amount of waste. As a result, other starting materials have been investigated for the development of more atom-economical esterifications. Aldehydes in the presence of alcohols can be oxidized directly to esters under aerobic conditions with a homogeneous NHC/iron catalyst[2] or heterogeneous gold catalysts.[3] More significantly, primary alcohols can also be employed as starting materials for the direct aerobic oxidation to esters. The oxidation can be accomplished with homogeneous iridium[4] and palladium[5] catalysts or with heterogeneous gold catalysts.[6] A different approach to the oxidation can be used under anaerobic conditions where ester formation is achieved by dehydrogenation of the alcohol. This transformation can be catalyzed by ruthenium,[7] iridium,[8] and rhodium[9] complexes, and the liberated hydrogen gas can be released from the reaction mixture or trapped with a stoichiometric scavenger such as a ketone or an olefin. The most attractive protocol is to perform the ester synthesis directly from a primary alcohol in the absence of a scavenger or an oxidant. This has so far been achieved with ruthenium CNN[7a] and PNN pincer complexes,[7c,d] $RuH_2(PPh_3)_4$,[7e] the Shvo catalyst,[7f] and an iridium PCP pincer complex.[8a] In addition, the special substrate butane-1,4-diol has been converted into γ-butyrolactone and hydrogen gas with homogeneous ruthenium catalysts[10] and heterogeneous copper catalysts.[11]

Recently, we have described a new dehydrogenative reaction for the synthesis of amides from primary alcohols and amines.[12,13] The amidation was catalyzed by the ruthenium NHC complex **1** (Figure 1) in the presence of PCy_3 and KO*t*Bu.[12] With less reactive amines, some self-condensation of the primary alcohol into the corresponding ester was observed as a byproduct, and we speculated about whether the conditions could be modified into a dehydrogenative ester synthesis. Herein, we describe a new ruthenium-catalyzed synthesis of esters from primary alcohols in which hydrogen gas is liberated.

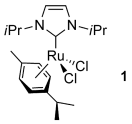


Figure 1. Structure of ruthenium NHC complex **1**.

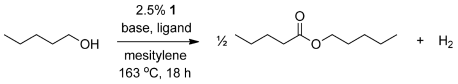
RESULTS AND DISCUSSION

For the initial studies, pentan-1-ol was selected as the test substrate and the reaction was performed in refluxing mesitylene under an argon atmosphere with 2.5% **1**. It was quickly realized that a base was essential for ester formation because almost no conversion occurred under neutral conditions (Table 1, entry 1). With KO*t*Bu, the yield of the ester increased when an increasing amount of the base was employed until a 58% yield was achieved with 20% KO*t*Bu (entries 2−6). Improved conversion was observed when a ligand such as PCy_3 was also added, where the best result was obtained with 10% KO*t*Bu and 2.5% PCy_3 (entries 7−9). A number of other bases were also tested, and KOH proved to be a better choice than KO*t*Bu for the esterification (entries 10−15). Under these conditions, the 92% yield of pentyl pentanoate was obtained with 10% KOH and 2.5% PCy_3 (entry 15). Other phosphine and amine ligands did not improve this result, and only tricyclopentylphosphine ($PCyp_3$) gave a comparable yield (entries 16−19). Varying the amount of PCy_3 from 2.5 to 9% showed that a near-quantitative yield

Received: October 4, 2011
Published: October 14, 2011

dx.doi.org/10.1021/om200928b | *Organometallics* 2011, 30, 6044−6048

Table 1. Synthesis of Pentyl Pentanoate from Pentan-1-ol



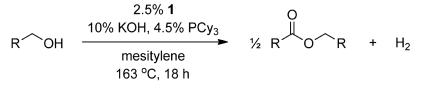
entry	base	% base	ligand	% ligand	yield (%)[a]
1	–	–	PCy_3	2.5	1
2	KO*t*Bu	7.5	–	–	19
3	KO*t*Bu	10	–	–	26
4	KO*t*Bu	15	–	–	50
5	KO*t*Bu	20	–	–	58
6	KO*t*Bu	28	–	–	51
7	KO*t*Bu	20	PCy_3	2.5	32
8	KO*t*Bu	10	PCy_3	2.5	70
9	KO*t*Bu	7.5	PCy_3	2.5	52
10	Et_3N	10	PCy_3	2.5	7
11	$NaHCO_3$	10	PCy_3	2.5	68
12	Na_2CO_3	10	PCy_3	2.5	56
13	K_2CO_3	10	PCy_3	2.5	71
14	NaOH	10	PCy_3	2.5	81
15	KOH	10	PCy_3	2.5	92
16	KOH	10	PPh_3	2.5	66
17	KOH	10	P*t*Bu_3	2.5	48
18	KOH	10	$PCyp_3$	2.5	90
19	KOH	10	DABCO	5	11
20	KOH	10	PCy_3	4.5	97
21	KOH	10	PCy_3	9	89
22[b]	KOH	10	PCy_3	4.5	90
23[c]	KOH	10	PCy_3	4.5	16

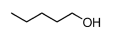
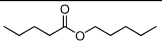
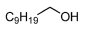
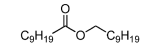
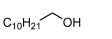
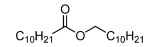
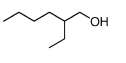
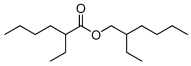
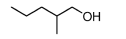
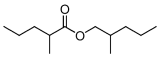
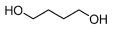
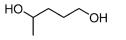
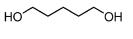
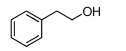
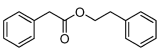
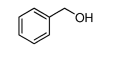
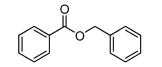
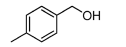
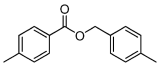
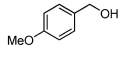
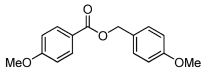
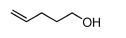
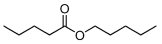
[a]GC yield. [b]With $[RuCl_2(IMe)(p\text{-cymene})]$. [c]With $[RuCl_2(p\text{-cymene})]_2$.

could be achieved with a slight excess of the phosphine as compared to the ruthenium complex (entries 20 and 21). The corresponding methyl-substituted carbene complex $[RuCl_2(IMe)(p\text{-cymene})]$ was also investigated, but a slightly lower yield was obtained in this case as compared to the yield with isopropyl complex **1** (entries 20 and 22). The importance of the carbene ligand was underlined by an experiment with the complex $[RuCl_2(p\text{-cymene})]_2$ where an only 16% yield of pentyl pentanoate was observed (entry 23). Thus, the optimal catalyst system for general use consists of complex **1** together with KOH and PCy_3 in refluxing mesitylene. Attempts to lower the reaction temperature by using a lower-boiling point solvent were not successful because reactions in toluene gave significantly lower yields while reactions in xylene were difficult to reproduce, although comparable yields were obtained in some cases. Experiments under neat conditions in the absence of a solvent also gave a lower yield because of the formation of several byproducts that were not further identified. The evolution of hydrogen during the reaction was confirmed by repeating the experiment in entry 20 with 1 mmol of pentan-1-ol. The reaction flask was connected to a measuring cylinder, and 17.5 mL was collected after 23 h. This corresponds to 0.73 mmol, and the gas was shown to be dihydrogen by using it for hydrogenating an alkyne in a separate experiment.

With the optimized catalyst system in place, our attention then shifted to other alcohols to investigate the scope of the dehydrogenative homodimerization (Table 2). Long chain aliphatic alcohols gave yields similar to those of pentan-1-ol (entries 1–3), whereas the yields with branched alcohols were somewhat lower (entries 4 and 5). The reaction with 2-

Table 2. Synthesis of Esters and Lactones from Alcohols and Diols



Entry	alcohol	product	yield (%)[c]
1			70 (97)
2			81 (86)
3			76 (84)
4			64 (63)[b]
5			45 (49)
6			71 (86)
7			78 (82)
8			61 (63)
9			48 (52)[c]
10			31 (27)
11			24[d]
12			19[e]
13			24[f] (13)

[a]Isolated yield (GC yield in parentheses). [b]Heptane (~3%) was also formed. [c]Toluene (7%) was also formed. [d]Toluene (63%) was also formed. [e]Anisole (48%) was also formed. [f]Inseparable mixture of saturated and unsaturated ester.

ethylhexan-1-ol in entry 4 was monitored over time, and the ester formed at the same rate as with pentan-1-ol in entry 1. However, a small amount of heptane (~3%) was observed as a byproduct, indicating that a competing decarbonylation[14] of the intermediate aldehyde is occurring with the branched alcohols. Lactonization of diols proceeded well under the esterification conditions as long as γ- and δ-lactones were formed (entries 6–8). The reaction in entry 6 was repeated under neat conditions with 1.25% **1** and gave a 60% isolated yield of γ-butyrolactone. Other lactone sizes, however, did not form easily under the

dx.doi.org/10.1021/om200928b | *Organometallics* 2011, 30, 6044–6048

conditions described in Table 2. Propane-1,3-diol afforded no β-propiolactone, while hexane-1,6-diol gave traces of ε-caprolactone; in both cases, large amounts of the starting diols did not react. 2-Phenylethanol gave the ester in 48% isolated yield together with a small amount of toluene (entry 9). Benzylic alcohols, however, gave very low yields of the corresponding benzoates (entries 10−12). Surprisingly, the decarbonylation turned out to be the major reaction in these cases. This limits the substrate scope to saturated alcohols because alcohols containing olefins are partially reduced by the liberated hydrogen (entry 13).

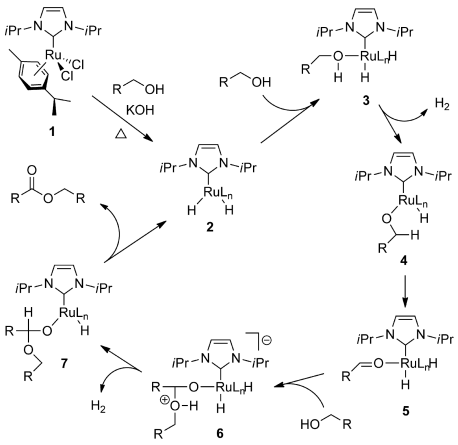
Attempts to couple two different alcohols were not successful. The reaction between ethanol and pentan-1-ol gave roughly a statistical mixture of all four possible ester products. It was subsequently shown that transesterification with primary alcohols occurs readily under the reaction conditions, which may further contribute to the poor selectivity in the cross esterification. The reaction between pentan-1-ol and benzyl alcohol also resulted in a mixture of all four ester products. When pentan-1-ol was reacted with propan-2-ol, 2-methylpropan-2-ol, or phenol, the only product was pentyl pentanoate from self-coupling of the primary alcohol and no cross esterification occurred with the secondary or tertiary alcohol or the phenol.

Several experiments were performed with special substrates to gain more information about the mechanism for the dehydrogenative esterification. When benzaldehyde was submitted to the standard conditions described in Table 2, the reaction gave only trace amounts of benzyl benzoate and benzyl alcohol. This rules out an aldehyde disproportionation mechanism, i.e., a Tishchenko reaction,[15] as the main pathway for ester formation. The same result was obtained with *p*-methoxybenzaldehyde where trace amounts of anisole were also formed. Because anisole was the main product in entry 12 of Table 2, this experiment suggests that decarbonylation does not happen directly from an aldehyde in solution, but rather from an aldehyde generated on ruthenium. When a 1:1 mixture of *p*-methylbenzaldehyde and benzyl alcohol was reacted under the standard conditions, an evenly distributed mixture of all four esters was observed together with *p*-methylbenzyl alcohol. Following the reaction over time showed that the four esters were formed at approximately the same rate and a relatively large amount of *p*-methylbenzyl alcohol was formed rather quickly. This indicates that the hydrogen gas liberated at the beginning of the reaction was used for reduction of *p*-methylbenzaldehyde and the alcohol then entered the catalytic cycle. On the basis of these experiments and the fact that aldehydes are not observed as byproducts in Table 2, we believe the ester is formed from the alcohol by a pathway that does not involve a free aldehyde in solution.

An experiment was also conducted with benzyl alcohol-α,α-d_2 to investigate a possible exchange of deuterium and hydrogen during the reaction. Interestingly, when the reaction was performed as described in entry 10 of Table 2, benzyl benzoate was obtained with 64% hydrogen and 36% deuterium in the benzylic position as judged by ^{1}H NMR. The experiment was conducted in mesitylene-d_{12}, and the hydrogen incorporation is therefore not a result of an exchange with the solvent. When the same esterification was stopped after 2.5 h and the starting alcohol reisolated, it turned out that complete scrambling of hydrogen and deuterium had occurred in the α-position. These experiments indicate that the initial β-hydride elimination to form benzaldehyde is a reversible reaction and, more significantly, that the catalytically active species is a ruthenium dihydride.

On the basis of these results and our previous studies of amidation,[12a] we propose the esterification mechanism in Scheme 1. Initially, the *p*-cymene ligand is lost, and the two

Scheme 1. Proposed Mechanism for Esterification



chloride ligands are replaced with hydride through alkoxide substitution and β-hydride elimination. The introduction of hydrides in this way has been shown earlier for other ruthenium(II) chloride complexes.[16] This generates ruthenium dihydride **2**, which is believed to be the catalytically active species. Coordination of the alcohol affords complex **3**, from which hydrogen gas is liberated by transfer of hydrogen to hydride as demonstrated previously.[17] This furnishes complex **4**, which upon β-hydride elimination yields aldehyde complex **5** where the carbonyl group can be σ- or π-coordinated to ruthenium.[18] Nucleophilic attack of the second molecule of alcohol then gives hemiacetal complex **6**. Transfer of hydrogen to hydride liberates the second molecule of hydrogen to give complex **7**, from which β-hydride elimination releases the ester product and regenerates active complex **2**. The scrambling of hydrogen and deuterium observed above can be explained by the fact that ruthenium dihydride complexes are known to scramble hydrogen and deuterium when subjected to hydrogen/deuterium gas.[19] Combined with a reversible β-hydride elimination, this provides a pathway by which OH group hydrogens can be transferred into the α-position of the alcohol.

In conclusion, we have described a new procedure for the dehydrogenative synthesis of esters from primary alcohols. The reaction is catalyzed by ruthenium NHC complex **1** and works most efficiently with linear aliphatic alcohols and 1,4-diols. A mechanism is proposed with a ruthenium dihydride species as the catalytically active component.

■ EXPERIMENTAL SECTION

General Information. All solvents were of HPLC grade and were not further purified. Column chromatography was performed on silica gel (0.015−0.040 mm). NMR chemical shifts were measured relative to the signals of residual $CHCl_3$ (δ_H 7.26) and $CDCl_3$ (δ_C 77.16).

General Procedure for Ruthenium-Catalyzed Ester Formation. $[RuCl_2(IiPr)(p\text{-cymene})]$[12a] (11.5 mg, 0.025 mmol), PCy_3 (12.6 mg, 0.045 mmol), and KOH (5.6 mg, 0.1 mmol) were placed in an oven-dried Schlenk flask. The flask was evacuated and refilled with argon three times. The primary alcohol (1 mmol; 0.5 mmol in the case of a diol) in anhydrous mesitylene (1 mL) was added and the reaction mixture refluxed for 18 h under an argon atmosphere. The mixture was cooled to room temperature and purified directly by dry column vacuum chromatography[20] (DCVC).

Pentyl Pentanoate. DCVC eluting with pentane containing 2% increments of ethyl acetate per fraction gave the product as a slightly yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92 (t, J = 6.7 Hz, 2H), 2.16 (t, J = 7.5 Hz, 2H), 1.62−1.40 (m, 4H), 1.32−1.11 (m, 6H), 0.91−0.70 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 64.4, 34.2, 28.4, 28.2, 27.2, 22.4, 22.4, 14.0, 13.8; MS m/z 173 $[M + H]^+$. NMR data are in accord with literature values.[21]

Decyl Decanoate. DCVC eluting with heptane containing 2% increments of ethyl acetate per fraction gave the product as a slightly yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.04 (t, J = 6.7 Hz, 2H), 2.27 (t, J = 7.5 Hz, 2H), 1.66−1.53 (m, 4H), 1.25 (m, 26H), 0.86 (t, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 64.5, 34.5, 32.0, 32.0, 29.7, 29.7, 29.6, 29.5, 29.4, 29.4, 29.4, 29.3, 28.8, 26.1, 25.2, 22.8, 22.8, 14.2, 14.2; MS m/z 312 $[M]^+$. NMR data are in accord with literature values.[22]

Undecyl Undecanoate. DCVC eluting with heptane containing 2% increments of ethyl acetate per fraction gave the product as a slightly yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.04 (t, J = 6.7 Hz, 2H), 2.27 (t, J = 7.5 Hz, 2H), 1.69−1.50 (m, 4H), 1.25 (bs, 30H), 0.86 (t, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 64.5, 34.5, 32.0, 29.8, 29.7, 29.7, 29.7, 29.6, 29.5, 29.5, 29.4, 29.4, 29.3, 28.8, 26.1, 25.2, 22.8, 14.2, 14.2; MS m/z 340 $[M]^+$. NMR data are in accord with literature values.[23]

2-Ethylhexyl 2-Ethylhexanoate. DCVC eluting with pentane containing 2% increments of ethyl acetate per fraction gave the product as a slightly yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.97 (d, J = 5.7 Hz, 2H), 2.31−2.17 (m, 1H), 1.64−1.10 (m, 17H), 0.95−0.69 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 66.3, 47.7, 38.9, 32.0, 30.6, 29.8, 29.0, 25.7, 24.0, 23.1, 22.8, 14.1, 14.0, 12.0, 11.1; MS m/z 257 $[M + H]^+$. NMR data are in accord with literature values.[23]

2-Methylpentyl 2-Methylpentanoate. DCVC eluting with pentane containing 2% increments of ethyl acetate per fraction gave the product as a slightly yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.01−3.88 (m, 1H), 3.87−3.79 (m, 1H), 2.42 (dt, J = 13.8, 7.0 Hz, 1H), 1.86−1.70 (m, 1H), 1.70−1.55 (m, 1H), 1.44−1.20 (m, 7H), 1.12 (d, J = 7.0 Hz, 3H), 0.95−0.79 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 69.2, 39.6, 39.6, 36.1, 35.7, 32.4, 20.5, 20.0, 17.2, 17.0, 17.0, 14.4, 14.1; MS m/z 201 $[M + H]^+$. NMR data are in accord with literature values.[24]

γ-Butyrolactone. DCVC eluting with heptane containing 10% increments of ethyl acetate per fraction gave the product as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.31 (t, J = 7.0 Hz, 2H), 2.50−2.41 (m, 2H), 2.29−2.17 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8, 68.6, 27.8, 22.2; MS m/z 86 $[M]^+$. NMR data are in accord with literature values.[25]

γ-Valerolactone. DCVC eluting with heptane containing 10% increments of ethyl acetate per fraction gave the product as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.62−4.50 (m, 1H), 2.50−2.43 (m, 2H), 2.35−2.23 (m, 1H), 1.82−1.68 (m, 1H), 1.32 (d, J = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 77.2, 29.6, 29.0, 21.0; MS m/z 100 $[M]^+$. NMR data are in accord with literature values.[25]

δ-Valerolactone. DCVC eluting with heptane containing 10% increments of ethyl acetate per fraction gave the product as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.21 (t, J = 5.9 Hz, 2H), 2.42 (t, J = 7.0 Hz, 2H), 1.88−1.65 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 69.3, 29.6, 22.1, 18.8; MS m/z 100 $[M]^+$. NMR data are in accord with literature values.[25]

Phenethyl 2-Phenylacetate. DCVC eluting with heptane containing 2% increments of ethyl acetate per fraction gave the product as a slightly yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.16 (m, 10H), 4.36 (t, J = 7.0 Hz, 2H), 3.65 (s, 2H), 2.96 (t, J = 7.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 137.8, 134.1, 129.4, 129.0, 128.6, 128.5, 127.1, 126.6, 65.4, 41.5, 35.1; MS m/z 104 $[C_8H_8]^+$. NMR data are in accord with literature values.[12a]

Benzyl Benzoate. DCVC eluting with heptane containing 2% increments of ethyl acetate per fraction gave the product as a slightly yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16−8.09 (m, 2H), 7.61−7.54 (m, 1H), 7.52−7.33 (m, 7H), 5.40 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 136.1, 133.1, 130.2, 129.8, 128.7, 128.4, 128.3, 128.2, 66.7; MS m/z 212 $[M]^+$. NMR data are in accord with literature values.[26]

4-Methylbenzyl 4-Methylbenzoate. DCVC eluting with heptane containing 2% increments of ethyl acetate per fraction gave the product as a slightly yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 5.32 (s, 2H), 2.41 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 143.8, 138.1, 133.3, 129.8, 129.4, 129.2, 128.4, 127.6, 66.6, 21.8, 21.3; MS m/z 240 $[M]^+$. NMR data are in accord with literature values.[8a]

4-Methoxybenzyl 4-Methoxybenzoate. DCVC eluting with heptane containing 2% increments of ethyl acetate per fraction gave the product as a slightly yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 9.0 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 3.4 Hz, 2H), 6.89 (d, J = 3.6 Hz, 2H), 5.27 (s, 2H), 3.84 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 163.5, 159.7, 131.8, 130.1, 128.5, 122.8, 114.0, 113.7, 66.4, 55.5, 55.4; MS m/z 272 $[M]^+$. NMR data are in accord with literature values.[5c]

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rm@kemi.dtu.dk.

■ ACKNOWLEDGMENTS

We thank the Danish Council for Independent Research—Technology and Production Sciences for financial support.

■ REFERENCES

(1) Otera, J.; Nishikido, J. *Esterification: Methods, Reactions, and Applications*; Wiley-VCH: Weinheim, Germany, 2010.

(2) Reddy, R. S.; Rosa, J. N.; Veiros, L. F.; Caddick, S.; Gois, P. M. P. *Org. Biomol. Chem.* **2011**, *9*, 3126.

(3) (a) Yasukawa, T.; Miyamura, H.; Kobayashi, S. *Chem. Asian J.* **2011**, *6*, 621. (b) Marsden, C.; Taarning, E.; Hansen, D.; Johansen, L.; Klitgaard, S. K.; Egeblad, K.; Christensen, C. H. *Green Chem.* **2008**, *10*, 168.

(4) (a) Arita, S.; Koike, T.; Kayaki, Y.; Ikariya, T. *Chem. Asian J.* **2008**, *3*, 1479. (b) Izumi, A.; Obora, Y.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2006**, *47*, 9199.

(5) (a) Luo, F.; Pan, C.; Cheng, J.; Chen, F. *Tetrahedron* **2011**, *67*, 5878. (b) Liu, C.; Wang, J.; Meng, L.; Deng, Y.; Li, Y.; Lei, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 5144. (c) Gowrisankar, S.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 5139.

(6) (a) Kaizuka, K.; Miyamura, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2010**, *132*, 15096. (b) Xu, B.; Haubrich, J.; Freyschlag, C. G.; Madix, R. J.; Friend, C. M. *Chem. Sci.* **2010**, *1*, 310. (c) Su, F.-Z.; Ni, J.; Sun, H.; Cao, Y.; He, H.-Y.; Fan, K.-N. *Chem.—Eur. J.* **2008**, *14*, 7131. (d) Nielsen, I. S.; Taarning, E.; Egeblad, K.; Madsen, R.; Christensen, C. H. *Catal. Lett.* **2007**, *116*, 35.

(7) (a) del Pozo, C.; Iglesias, M.; Sánchez, F. *Organometallics* **2011**, *30*, 2180. (b) Owston, N. A.; Nixon, T. D.; Parker, A. J.; Whittlesey, M. K.; Williams, J. M. J. *Synthesis* **2009**, 1578. (c) Zhang, J.; Gandelman, M.; Shimon, L. J. W.; Milstein, D. *Dalton Trans.* **2007**, 107. (d) Zhang, J.; Leitus, G.; Ben-David, Y.; Milstein, D. *J. Am. Chem.*

Soc. **2005**, *127*, 10840. (e) Murahashi, S.-I.; Naota, T.; Ito, K.; Maeda, Y.; Taki, H. *J. Org. Chem.* **1987**, *52*, 4319. (f) Blum, Y.; Shvo, Y. *J. Organomet. Chem.* **1985**, *282*, C7.
(8) (a) Musa, S.; Shaposhnikov, I.; Cohen, S.; Gelman, D. *Angew. Chem., Int. Ed.* **2011**, *50*, 3533. (b) Yamamoto, N.; Obora, Y.; Ishii, Y. *J. Org. Chem.* **2011**, *76*, 2937. (c) Suzuki, T.; Matsuo, T.; Watanabe, K.; Katoh, T. *Synlett* **2005**, 1453.
(9) Zweifel, T.; Naubron, J.-V.; Grützmacher, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 559.
(10) Zhao, J.; Hartwig, J. F. *Organometallics* **2005**, *24*, 2441.
(11) (a) Hwang, D. W.; Kashinathan, P.; Lee, J. M.; Lee, J. H.; Lee, U.-h.; Hwang, J.-S.; Hwang, Y. K.; Chang, J.-S. *Green Chem.* **2011**, *13*, 1672. (b) Mikami, Y.; Ebata, K.; Mitsudome, T.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K. *Heterocycles* **2010**, *80*, 855. (c) Ichikawa, N.; Sato, S.; Takahashi, R.; Sodesawa, T.; Inui, K. *J. Mol. Catal. A: Chem.* **2004**, *212*, 197.
(12) (a) Dam, J. H.; Osztrovszky, G.; Nordstrøm, L. U.; Madsen, R. *Chem.—Eur. J.* **2010**, *16*, 6820. (b) Nordstrøm, L. U.; Vogt, H.; Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*, 17672.
(13) See also: Chen, C.; Hong, S. H. *Org. Biomol. Chem.* **2011**, *9*, 20.
(14) Fristrup, P.; Kreis, M.; Palmelund, A.; Norrby, P.-O.; Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*, 5206.
(15) Simon, M.-O.; Darses, S. *Adv. Synth. Catal.* **2010**, *352*, 305.
(16) (a) Solari, E.; Gauthier, S.; Scopelliti, R.; Severin, K. *Organometallics* **2009**, *28*, 4519. (b) Aranyos, A.; Csjernyik, G.; Szabo, K. J.; Bäckvall, J.-E. *Chem. Commun.* **1999**, 351.
(17) Chatwin, S. L.; Davidson, M. G.; Doherty, C.; Donald, S. M.; Jazzar, R. F. R.; Macgregor, S. A.; McIntyre, G. J.; Mahon, M. F.; Whittlesey, M. K. *Organometallics* **2006**, *25*, 99.
(18) Bosson, J.; Poater, A.; Cavallo, L.; Nolan, S. P. *J. Am. Chem. Soc.* **2010**, *132*, 13146.
(19) Burling, S.; Kociok-Köhn, G.; Mahon, M. F.; Whittlesey, M. K.; Williams, J. M. J. *Organometallics* **2005**, *24*, 5868.
(20) Pedersen, D. S.; Rosenbohm, C. *Synthesis* **2001**, 2431.
(21) Kapustina, N. I.; Sokova, L. L.; Makhaev, V. D.; Borisov, A. P.; Nikishin, G. I. *Russ. Chem. Bull., Int. Ed.* **2000**, *49*, 1842.
(22) Khusnutdinov, R. I.; Shchadneva, N. A.; Baiguzina, A. R.; Lavrentieva, Y. Y.; Dzhemilev, U. M. *Russ. Chem. Bull., Int. Ed.* **2002**, *51*, 2074.
(23) Nikishin, G. I.; Sokova, L. L.; Kapustina, N. I. *Russ. Chem. Bull., Int. Ed.* **2009**, *58*, 303.
(24) Morita, K.-I.; Nishiyama, Y.; Ishii, Y. *Organometallics* **1993**, *12*, 3748.
(25) Mitsudome, T.; Noujima, A.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K. *Green Chem.* **2009**, *11*, 793.
(26) Hans, J. J.; Driver, R. W.; Burke, S. D. *J. Org. Chem.* **2000**, *65*, 2114.

Bibliography

[1] IUPAC, *Compendium of Chemical Terminology*, v. 2.3.2, **2012**.

[2] Berzelius, J. J., *Årsberättelse om Framstegen i Fysik och Kemi*, Royal Swedish Academy of Science, Stockholm **1835**.

[3] Roberts, M. W.; *Catal. Lett.* **2000**, 67, 1–4.

[4] van Santen, R.; in *Catalysis: From Principles to Applications*; Eds. Beller, M.; Renken, A; van Santen, R.; Wiley-VCH Verlag GmbH & Co. KGaA, **2012**, chapter 1, 3–19.

[5] Lindström, B.; Petterson, L. J.; *Cattech.* **2003**, 7, 130–138.

[6] Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V.; *Angew. Chem. Int. Ed.* **2012**, 51, 5062–5085.

[7] Mizoroki, T.; Mori, K.; Ozaki, A.; *Bull. Chem. Soc. Jpn.* **1971**, 44, 581–581. Heck, R. F.; Nolley, Jr., J. P.; *J. Org. Chem.* **1972**, 37, 2320–2322.

[8] Sonogashira, K.; Tohda, Y.; Hagihara, N.; *Tetrahedron Lett.* **1975**, 50, 4467–4470.

[9] King, A. O.; Okukado, N.; Negishi, E.-I.; *J. Chem. Soc., Chem. Commun.* **1977**, 683–684.

[10] Milstein, D.; Stille, J. K.; *J. Am. Chem. Soc.* **1978**, 100, 3636–3638. Kosugi, M.; Shimizu, Y.; Migita, T.; *Chem. Lett.* **1977**, 6, 1423–1424. Azarian, D.; Dua, S. S.; Eaborn, C.; Walton, D. R. M.; *J. Organomet. Chem.* **1976**, 117, C55–C57.

[11] Miyaura, N.; Yamada, K.; Suzuki, A.; *Tetrahedron Lett.* **1979**, 20, 3437–3440.

[12] Roughley, S. D.; Jordan, A. M.; *J. Med. Chem.* **2011**, 54, 3451–3479.

[13] Collins, T. J.; in *Green Chemistry, Macmillan Encyclopedia of Chemistry*; Simon and Schuster Macmillan; New York, **1997**, vol. 2, 691–697.

[14] Anastas, P. T.; Kirchhoff, M. M.; Williamson, T. C.; *Appl. Catal. A-Gen.* **2001**, 221, 3–13.

[15] Trost, B. M.; *Science* **1991**, 254, 1471–1477.

[16] Czaplik, W. M.; Mayer, M.; Cvengroš, J.; von Wangelin, A. J.; *ChemSusChem* **2009**, 2, 396–417.

[17] Rao, H.; Fu, H.; *Synlett.* **2011**, 745–769.

[18] Cahiez, G.; Moyeux, A.; *Chem. Rev.* **2010**, 110, 1435–1462.

[19] Anastas, P.; Eghbali, N.; *Chem. Soc. Rev.* **2010**, 39, 301–312.

[20] Gunanathan, C.; Milstein, D.; *Science* **2013**, 341, 249–260. Choi, J.; MacArthur, A. H. R.; Brookhart, M.; Goldman, A. S.; *Chem. Rev.* **2011**, 111, 1761–1779. Dobereiner, G. E.; Crabtree, R. H.; *Chem. Rev.* **2010**, 110, 681–703. Chen, C.; Hong, S. H.; *Org. Biomol. Chem.* **2011**, 9, 20–26.

[21] Nielsen, M.; Junge, H.; Kammer, A.; Beller, M.; *Angew. Chem. Int. Ed.* **2012**, 51, 5711–5713.

[22] Gunanathan, C.; Ben-David, Y.; Milstein, D.; *Science* **2007**, 317, 790–792.

[23] Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J.; *Adv. Synth. Catal.* **2007**, 349, 1555–1575. Fujita, K.-i.; Yamaguchi, R.; *Synlett.* **2005**, 560–571.

[24] Naota, T.; Murahashi, S.-I.; *Synlett.* **1991**, 693–693.

[25] Zhang, J.; Leitus, G.; Ben-David, Y.; Milstein, D.; *J. Am. Chem. Soc.* **2005**, 127, 10840–10841.

[26] Nordstrøm, L. U.; Vogt, H.; Madsen, R.; *J. Am. Chem. Soc.* **2008**, 130, 17672–17673.

[27] Dam, J. H.; Osztrovszky, G.; Nordstrøm, L. U.; Madsen, R.; *Chem. Eur. J.* **2010**, 16, 6820–6827.

[28] Delaude, L.; Delfosse, S.; Richel, A.; Demonceau, A.; Noels, A. F.; *Chem. Commun.* **2003**, 1526–1527.

[29] Ghosh, S. C.; Muthaiah, S.; Zhang, Y.; Xu, X.; Hong, S. H.; *Adv. Synth. Catal.* **2009**, 351, 2643–2649.

[30] Ghosh, S. C.; Hong, S. H.; *Eur. J. Org. Chem.* **2010**, 4266–4270.

[31] Muthaiah, S.; Ghosh, S. C.; Jee, J.-E.; Chen, C.; Zhang, J.; Hong, S. H.; *J. Org. Chem.* **2010**, 75, 3002–3006.

[32] Watson, A. J. A.; Maxwell, A. C.; Williams, J. M. J.; *Org. Lett.* **2009**, 11, 2667–2670.

[33] Zweifel, T.; Naubron, J.-V.; Grützmacher, H.; *Angew. Chem. Int. Ed.* **2009**, 48, 559–563.

[34] Shimizu, K.-i.; Ohshima, K.; Satsuma, A.; *Chem. Eur. J.* **2009**, 15, 9977–9980.

[35] Schleker, P. P. M.; Honeker, R. Klankermayer, J.; Leitner, W.; *ChemCatChem* **2013**, 5, 1762–1764.

[36] Maggi, A.; Madsen, R.; *Organometallics* **2012**, 31, 451–455.

[37] Gnanaprakasam, B.; Zhang, J.; Milstein, D.; *Angew. Chem. Int. Ed.* **2010**, 49, 1468–1471.

[38] Esteruelas, M. A.; Honczek, N.; Oliván, M.; Oñate, E.; Valencia, M.; *Organometallics* **2011**, 30, 2468–2471.

[39] Makarov, I. S.; Fristrup, P.; Madsen, R.; *Chem. Eur. J.* **2012**, 18, 15683–15692.

[40] Sølvhøj, A.; Madsen, R.; *Organometallics* **2011**, 30, 6044–6048.

[41] Fristrup, P.; Tursky, M.; Madsen, R.; *Org. Biomol. Chem.* **2012**, 10, 2569–2577.

[42] Fujita, K.-i.; Enoki, Y.; Yamaguchi, R.; *Tetrahedron* **2008**, 64, 1943–1954.

[43] Solari, E.; Gauthier, S.; Scopelliti, R.; Severin, K.; *Organometallics* **2009**, 28, 4519–4526. Aranyos, A.; Csjernyik, G.; Szabó, K. J.; Bäckvall, J.-E.; *Chem. Commun.* **1999**, 351–352.

[44] Otera, J.; *Esterification: Methods, Reactions and Applications*, **2003**, Wiley-VCH GmbH & Co. KGaA, Weinheim.

[45] Fischer, E.; Speier, A.; *Ber. Dtsch. Chem. Ges.* **1895**, 28, 3252–3258.

[46] Neises, B.; Steglich, W.; *Angew. Chem. Int. Ed.* **1978**, 17, 522–524.

[47] Mitsunobu, O.; Yamada, M.; *B. Chem. Soc. Jpn.* **1967**, 40, 2380–2382.

[48] Tormakangas, O. P.; Koskinen, A. M. P.; in *Recent Research Developments in Organic Chemistry, vol. 5*; Ed. Pandalai, S. G.; Transword Research Network **2001**, 225–255.

[49] Geissman, T. A.; in *Organic Reactions, vol. 2*; Eds. Adams, R. et. al.; John Wiley & sons inc.; New York **1944**, 94–113.

[50] Meerwein, H.; Schmidt, R.; *Liebigs Ann. Chem.* **1925**, 444, 221–238. Verley, A.; *Bull. Soc. Chim. Fr.* **1925**, 37, 537–542. Verley, A.; *Bull. Soc. Chim. Fr.* **1925**, 37, 871–874. Ponndorf, W.; *Angew. Chem.* **1926**, 39, 138–143.

[51] Oppenauer, R. V.; *Recl. Trav. Chim. Pays-Bas* **1937**, 56, 137–144.

[52] Kende, A. S.; in *Organic Reactions, vol. 11*; Eds. Adams, R. et. al.; John Wiley & sons inc.; New York **1960**, 261–316.

[53] Baeyer, A.; Villiger, V.; *Ber. Dtsch. Chem. Ges.* **1899**, 32, 3625–3633. Baeyer, A.; Villiger, V.; *Ber. Dtsch. Chem. Ges.* **1900**, 33, 858–864.

[54] Doering, W. v. E.; Speers, L.; *J. Am. Chem. Soc.* **1950**, 72, 5515–5518.

[55] Blum, Y.; Reshef, D.; Shvo, Y.; *Tetrahedron Lett.* **1981**, 22, 1541–1544. Blum, Y.; Shvo, Y.; *J. Organomet. Chem.* **1984**, 263, 93–107.

[56] Blum, Y.; Shvo, Y.; *J. Organomet. Chem.* **1985**, 282, C7–C10.

[57] Murahashi, S.-I.; Ito, K.; Naota, T.; Maeda, Y.; *Tetrahedron Lett.* **1981**, 22, 5327–5330. Murahashi, S.-I.; Naota, T.; Ito, K.; Maeda, Y.; Taki, H.; *J. Org. Chem.* **1987**, 52, 4319–5327.

[58] Zhang, J.; Gandelman, M.; Shimon, L. J. W.; Rozenberg, H.; Milstein, D.; *Organometallics* **2004**, 23, 4026–4033.

[59] Owston, N. A.; Nixon, T. D.; Parker, A. J.; Whittlesey, M. K.; Williams, J. M. J.; *Synthesis*, **2009**, 1578–1581.

[60] del Pozo, C.; Iglesias, M.; Sánchez, F.; *Organometallics* **2011**, 30, 2180–2188.

[61] Suzuki, T.; Matsuo, T.; Watanabe, K.; Katoh, T.; *Synlett.* **2005**, 1453–1455.

[62] Yamamoto, N.; Obora, Y.; Ishii, Y.; *J. Org. Chem.* **2011**, 76, 2937–2941.

[63] Musa, S.; Shaposhnikov, I.; Cohen, S.; Gelman, D.; *Angew. Chem. Int. Ed.* **2011**, 50, 3533–3537.

[64] Makarov, I. S.; *Ruthenium-Catalyzed Transformations of Alcohols: Mechanistic Investigations and Methodology Development*, PhD Thesis March **2013**, Technical University of Denmark.

[65] Makarov, I. S.; Madsen, R.; *J. Org. Chem.* **2013**, 78, 6593–6598.

[66] Netherton, M. R.; Fu, G. C.; *Org. Lett.* **2001**, 3, 4295–4298.

[67] Pedersen, D. S.; Rosenbohm, C.; *Synthesis* **2001**, 2431–2434.

[68] Felpin, F.-X.; Fouquet, E.; *Chem. Eur. J.* **2010**, 16, 12440–12445.

[69] Gottlieb, H. E.; Kotlyar, V.; Nudelman, A.; *J. Org. Chem.* **1997**, 62, 7512–7515.

[70] Kapustina, N. I.; Sokova, L. L.; Makhaev, V. D.; Borisov, A. P.; Nikishin, G. I.; *Russ. Chem. Bull., Int. Ed.* **2000**, 49(11), 1842–1845.

[71] Khusnutdinov, R. I.; Shchadneva, N. A.; Baiguzina, A. R.; Lavrentieva, Y. Y.; Dzhemilev, U. M.; *Russ. Chem. Bull., Int. Ed.* **2002**, 51(11), 2074–2079.

[72] Nikishin, G. I.; Sokova, L. L.; Kapustina, N. I.; *Russ. Chem. Bull., Int. Ed.* **2009**, 58(2), 303–308.

[73] Morita, K.-I.; Nishiyama, Y.; Ishii, Y.; *Organometallics* **1993**, 12, 3748–3752.

[74] Mitsudome, T.; Noujima, A.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K.; *Green Chem.* **2009**, 11, 793–797.

[75] Hans, J. J.; Driver, R. W.; Burke, S. D.; *J. Org. Chem.* **2000**, 65, 2114–2121.

[76] Gowrisankar, S.; Neumann, H.; Beller, M.; *Angew. Chem. Int. Ed.* **2011**, 50, 5139–5143.

[77] Werner, T.; Koch, J.; *Eur. J. Org. Chem.* **2010**, 6904–6907.

[78] Bong, D. T. Y.; Chan, E. W. L.; Diercks, R.; Dosa, P. I.; Haley, M. M.; Matzger, A. J.; Miljanić, O. Š.; Vollhardt, K. P. C.; Bond, A. D.; Teat, S. J; Stanger, A.; *Org. Lett.* **2004**, 6, 2249–2252.

[79] Stanger, A.; *Chem. Commun.* **2009**, 1939–1947.

[80] Faraday, M.; *Phil. Trans. R. Soc. Lond.* **1825**, 115, 440–466.

[81] Kekulé, A.; *Bull. Soc. Chim. Fr.* **1865**, 3, 98–110.

[82] Kekulé, A.; *Liebigs Ann. Chem.* **1866**, 137, 129–196.

[83] Erlenmeyer, E.; *Liebigs Ann. Chem.* **1866**, 137, 327–359.

[84] Schleyer, P. R. S.; Jiao, H.; *Pure & Appl. Chem.* **1996**, 68, 209–218.

[85] Randić, M.; *Chem. Rev.* **2003**, 103, 3449–3605.

[86] Diercks, R.; Vollhardt, K. P. C.; *J. Am. Chem. Soc.* **1986**, 108, 3150–3152.

[87] Hückel, E.; *Z. Phys.* **1931**, 70, 204–286.

[88] Shaik, S. S.; Bar, R.; *New J. Chem.* **1984**, 8, 411–420.

[89] Lothrop, W. C.; *J. Am. Chem. Soc.* **1941**, 63, 1187–1191.

[90] Hosaeus, W.; *Monatsh. Chem.* **1893**, 14, 323–332.

[91] Shepherd, M. K.; *Cyclobutarenes: The Chemistry of Benzocyclobutene, Biphenylene, and Related Compounds*, **1991**, Elsevier, chapter 4.

[92] Berris, B. C.; Hovakeemian, G. H.; Lai, Y.-H.; Mestdagh, H.; Vollhardt, K. P. C.; *J. Am. Chem. Soc.* **1985**, 107, 5670–5687.

[93] Waser, J.; Lu, C.-S.; *J. Am. Chem. Soc.* **1944**, 66, 2035–2042. Mak, T. C. W.; Trotter, J.; *J. Chem. Soc.* **1962**, 1–8. Fawcett, J. K.; Trotter, J.; *Acta Crystallogr.* **1966**, 20, 87–93. Yokozeki, A.; Wilcox Jr., C. F.; Bauer, S. H.; *J. Am. Chem. Soc.* **1974**, 96, 1026–1032.

[94] Kabir, S. M. H.; Hasegawa, M.; Kuwatani, Y.; Yoshida, M.; Matsuyama, H.; Iyoda, M.; *J. Chem. Soc. Perkin Trans. 1* **2001**, 159–165.

[95] Shepherd, M. K.; *Cyclobutarenes: The Chemistry of Benzocyclobutene, Biphenylene, and Related Compounds*, **1991**, Elsevier, chapter 5.

[96] Blatchly, J.; Taylor, R.; *J. Chem. Soc. B.* **1968**, 1402–1403.

[97] Cava, M. P.; Mitchell, M. J.; *Cyclobutadiene and related compounds*, **1967**, Academic Press N.Y., Org. Chem. Monographs vol. 10.

[98] Streitwieser, Jr., A.; Ziegler, G. R.; Mowery, P. C.; Lewis, A.; Lawler, R. G.; *J. Am. Chem. Soc.* **1968**, 90, 1357–1358.

[99] Heaney, H.; Mason, K. G.; Sketchley, J. M.; *Tetrahedron Lett.* **1970**, 11, 7, 485–488.

[100] Baker, W.; Boarland, Miss M. P. V.; McOmie, J. F. W.; *J. Chem. Soc.* **1954**, 1476–1482.

[101] Friedman, L.; Lindow, D. F.; *J. Am. Chem. Soc.* **1968**, 90, 2324–2328.

[102] Droske, J. P.; Stille, J. K.; *Macromolecules* **1984**, 17, 1–10. Gaidis, J. M.; *J. Org. Chem.* **1970**, 35, 2811–2813. Ecker, A.; Schmidt, U.; *Monatsh. Chem.* **1971**, 102, 1851–1854.

[103] Barton, J. W.; Walker, R. B.; *Tetrahedron Lett.* **1978**, 11, 1005–1008.

[104] Diercks, R.; Vollhardt, K. P. C.; *Angew. Chem.* **1986**, 98, 268–270.

[105] Miljanić, O. Š.; Vollhardt, K. P. C.; in *Carbon-Rich Compounds: From Molecules to Materials*; Eds. Haley, M. M.; Tykwinski, R. R.; Wiley-VCH: Weinheim; **2006**, chapter 4, 140–197.

[106] Bong, D. T. Y.; Gentric, L.; Holmes, D.; Matzger, A. J.; Scherhag, F.; Vollhardt, K. P. C.; *Chem. Commun.* **2002**, 278–279.

[107] Eickmeier, C.; Holmes, D.; Junga, H.; Matzger, A. J.; Scherhag, F.; Shim, M.; Vollhardt, K. P. C.; *Angew. Chem. Int. Ed.* **1999**, 38, 800–804.

[108] Hirthammer, M.; Vollhardt, K. P. C.; *J. Am. Chem. Soc.* **1986**, 108, 2482–2484.

[109] Schmidt-Radde, R. H.; Vollhardt, K. P. C.; *J. Am. Chem. Soc.* **1992**, 114, 9713–9715.

[110] Blanco, L.; Helson, H. E.; Hirthammer, M.; Mestdagh, H.; Spyroudis, S.; Vollhardt, K. P. C.; *Angew. Chem.* **1987**, 99, 1276–1277. Boese, R.; Matzger, A. J.; Mohler, D. L.; Vollhardt, K. P. C.; *Angew. Chem. Int. Ed.* **1995**, 34, 1478–1481. Mohler, D. L.; Kumaraswamy, S.; Stanger, A.; Vollhardt, K. P. C.; *Synlett.* **2006**, 2981–2984.

[111] Han, S.; Anderson, D. R.; Bond, A. D.; Chu, H. V.; Disch, R. L.; Holmes, D.; Schulman, J. M.; Teat, S. J.; Vollhardt, K. P. C.; Whitener, G. D.; *Angew. Chem. Int. Ed.* **2002**, 41, 3227–3230.

[112] Gilman, H.; Gaj, B. J.; *J. Org. Chem.* **1957**, 22, 447–449.

[113] Cracknell, M. E.; Kabli, R. A.; McOmie, J. F. W.; Perry, D. H.; *J. Chem. Soc. Perkin Trans. 1* **1985**, 115–120.

[114] Mitchell, R. H.; Lai, Y.-H.; Williams, R. V.; *J. Org. Chem.* **1979**, 44, 4733–4735.

[115] Dosa, P. I.; Gu, Z.; Hager, D.; Karnev, W. L.; Vollhardt, K. P. C.; *Chem. Commun.* **2009**, 1967–1969.

[116] Leroux, F. R.; Bonnafoux, L.; Heiss, C.; Colobert, F.; Lanfranchi, D. A.; *Adv. Synth. Catal.* **2007**, 349, 2705–2713.

[117] Schaub, T.; Radius, U.; *Tetrahedron Lett.* **2005**, 46, 8195–8197.

[118] Heck, R. F.; Nolley, Jr., J. P.; *J. Org. Chem.* **1972**, 37, 2320–2322.

[119] Dieck, H.; Heck, F.; *J. Organomet. Chem.* **1975**, 93, 259–263.

[120] Cassar, L.; *J. Organomet. Chem.* **1975**, 93, 253–257.

[121] Negishi, E.-I.; Anastasia, L.; *Chem. Rev.* **2003**, 103, 1979–2017.

[122] Chinchilla, R.; Nájera, C.; *Chem. Soc. Rev.* **2011**, 40, 5084–5121.

[123] Chinchilla, R.; Nájera, C.; *Chem. Rev.* **2007**, 107, 874–922.

[124] Elangovan, A.; Wang, Y.-H.; Ho, T.-I.; *Org. Lett.* **2003**, 5, 1841–1844.

[125] Thorand, S.; Krause, N.; *J. Org. Chem.* **1998**, 63, 8551–8553.

[126] Berthelot, M.; *C. R. Acad. Sci.* **1866**, 62, 905.

[127] Reppe, W.; Schweckendiek, W. J.; *Liebigs Ann. Chem.* **1948**, 560, 104–116.

[128] Gandon, V.; Aubert, C.; Malacria, M.; *Chem. Commun.* **2006**, 2209–2217.

[129] Lautens, M.; Klute, W.; Tam, W.; *Chem. Rev.* **1996**, 96, 49–92.

[130] Vollhardt, K. P. C.; Bergman, R. G.; *J. Am. Chem. Soc.* **1974**, 96, 4996–4998.

[131] Funk, R. L.; Vollhardt, K. P. C.; *J. Am. Chem. Soc.* **1980**, 102, 5253–5261.

[132] Hegedus, L. S.; Söderberg, B. C. G.; *Transition Metals in the Synthesis of Complex Organic Molecules*, 3rd Edition, University Science Books, **2010**, p 333.

[133] Miyake, Y.; Wu, M.; Rahman, M. J.; Kuwatani, Y.; Iyoda, M.; *J. Org. Chem.* **2006**, 71, 6110–6117.

[134] Parsons, A. F.; *An Introduction to Free Radical Chemistry*, **2000**, Blackwell Science Ltd., Oxford.

[135] Gomberg, M.; *J. Am. Chem. Soc.* **1900**, 22, 757–771.

[136] Matthews, D. P.; McCarthy, J. R.; *J. Org. Chem.* **1990**, 55, 2973–2975.

[137] Gevorgyan, V.; Priede, E.; Liepiņš, E.; Gavars, M.; Lukevics, E.; *J. Organomet. Chem.* **1990**, 393, 333–338.

[138] Cao, K.; Jiang, Y.-J.; Zhang, S.-Y.; Fan, C.-A.; Tu, Y.-Q.; Pan, Y.-J.; *Tetrahedron Lett.* **2008**, 49, 4652–4654.

[139] Yoshimitsu, T.; Tsunoda, M.; Nagaoka, H.; *Chem. Commun.* **1999**, 1745–1746.

[140] Yoshimitsu, T.; Arano, Y.; Nagaoka, H.; *J. Org. Chem.* **2003**, 68, 625–627.

[141] Yamada, K.-i.; Fujihara, H.; Yamamoto, Y.; Miwa, Y.; Taga, T.; Tomioka, K.; *Org. Lett.* **2002**, 4, 3509–3511.

[142] Bertrand, M. P.; Coantic, S.; Feray, L.; Nouguier, R.; Perfetti, P.; *Tetrahedron* **2000**, 56, 3951–3961.

[143] Yamada, K.-i.; Yamamoto, Y.; Tomioka, K.; *Org. Lett.* **2003**, 5, 1797–1799. Yamada, K.-i.; Yamamoto, Y.; Tomioka, K.; *J. Syn. Org. Chem. Jpn.* **2004**, 62, 1158–1165.

[144] Chen, Z.; Zhang, Y.-X.; An, Y.; Song, X.-L.; Wang, Y.-H.; Zhu, L.-L.; Guo, L.; *Eur. J. Org. Chem.* **2009**, 5146–5152.

[145] Jang, Y.-J.; Shih, Y.-K.; Liu, J.-Y.; Kuo, W.-Y.; Yao, C.-F.; *Chem. Eur. J.* **2003**, 9, 2123–2128.

[146] Yao, C.-F.; Chu, C.-M.; Liu, J.-T.; *J. Org. Chem.* **1998**, 63, 719–722.

[147] Liu, J.-T.; Jang, Y.-J.; Shih, Y.-K.; Hu, S.-R.; Chu, C.-M.; Yao, C.-F.; *J. Org. Chem.* **2001**, 66, 6021–6028.

[148] Jang, Y.-J.; Yan, M.-C.; Lin, Y.-F.; Yao, C.-F.; *J. Org. Chem.* **2004**, 69, 3961–3963.

[149] Gilbert, B. C.; Harrison, R. J.; Lindsay, C. I.; McGrail, P. T.; Parsons, A. F.; Southward, R.; Irvine, D. J.; *Macromolecules* **2003**, 36, 9020–23.

[150] Snider, B. B.; *Chem. Rev.* **1996**, 339–363.

[151] Jahn, U.; *Top. Curr. Chem.* **2012**, 320, 121–190.

[152] Abel, E. W.; Stone, F. G. A.; Wilkinson, G.; *Comprehensive Organometallic Chemistry II, Vol. 6: Manganese Group*, 1. Ed., Elsevier, **1995**.

[153] Meyer, T. J.; Caspar, J. V.; *Chem. Rev.* **1985**, 85, 187–218.

[154] Gilbert, B. C.; Kalz, W.; Lindsay, C. I.; McGrail, P. T.; Parsons, A. F.; Whittaker, D. T. E.; *J. Chem. Soc. Perkin Trans. 1* **2000**, 1187–1194. Gilbert, B. C.; Kalz, W.; Lindsay, C. I.; McGrail, P. T.; Parsons, A. F.; Whittaker, D. T. E.; *Tetrahedron Lett.* **1999**, 6095–6098.

[155] Friestad, G. K.; Marié, J.-C.; Suh, Y.; Qin, J.; *J. Org. Chem.* **2006**, 71, 7016–7027.

[156] Kondo, T.; Tsuji, Y.; Watanabe, Y.; *Tetrahedron Lett.* **1988**, 29, 3833–3836.

[157] Fukuyama, T.; Nishitani, S.; Inouye, T.; Morimoto, K.; Ryu, I.; *Org. Lett.* **2006**, 8, 1383–1386.

[158] Kondo, T.; Sone, Y.; Tsuji, Y.; Watanabe, Y.; *J. Organomet. Chem.* **1994**, 473, 163–173.

[159] Nakao, J.; Inoue, R.; Shinokubo, H.; Oshima, K.; *J. Org. Chem.* **1997**, 62, 1910–1911.

[160] Tayama, O.; Nakano, A.; Iwahama, T.; Sakaguchi, S.; Ishii, Y.; *J. Org. Chem.* **2004**, 69, 5494–5496. Nohair, K.; Lachaise, I.; Paugam, J.-P.; Nédélec, J.-Y.; *Tetrahedron Lett.* **1992**, 33, 213–216.

[161] "Platinum Today" http://www.platinum.matthey.com/applications/

[162] "2011 Minerals Yearbook; Platinum Group Metals" http://minerals.usgs.gov/minerals/pubs/commodity/platinum/myb1-2011-plati.pdf

[163] "Guideline on the Specification Limits for Residues of Metal Catalysts or Metal Reagents", European Medicines Agency, London, 17 February **2008**, http://www.ema.europa.eu/ema.

[164] Magano, J.; Dunetz, J. R.; *Chem. Rev.* **2011**, 111, 2177–2250.

[165] Santamaria, A. B.; Sulsky, S. I.; *J. Toxicol. Environ. Health, A.* **2010**, 73, 128–155.

[166] Alami, M.; Ramiandrasoa, P.; Cahiez, G.; *Synlett.* **1998**, 325–327.

[167] Cahiez, G.; Lepifre, F.; Ramiandrasoa, P.; *Synthesis*, **1999**, 2138–2144.

[168] Cahiez, G.; Gager, O.; Lecomte, F.; *Org. Lett.* **2008**, 10, 5255–5256.

[169] Rueping, M.; Ieawsuwan, W.; *Synlett.* **2007**, 247–250.

[170] Teo, Y.-C.; Yong, F.-F.; Poh, C.-Y.; Yan, Y.-K.; Chua, G.-L.; *Chem. Commun.* **2009**, 6258–6260.

[171] Yong, F.-F.; Teo, Y.-C.; *Tetrahedron Lett.* **2010**, 51, 3910–3912.

[172] Yong, F.-F.; Teo, Y.-C.; *Synlett.* **2012**, 2106–2110.

[173] Teo, Y.-C.; Yong, F.-F.; Ithnin, I. K.; Yio, S.-H. T.; Lin, Z.; *Eur. J. Org. Chem.* **2013**, 515–524.

[174] Iyer, S.; Thakur, V. V.; *J. Mol. Catal. A: Chem.* **2000**, 157, 275–278.

[175] Urushibara, Y.; *Ann. N. Y. Acad. Sci.* **1967**, 145, 52–57.

[176] Qiao, J.; Zhu, W.; Zhuo, G.; Zhou, H.; Jiang, X.; *Chin. J. Catal.* **2008**, 29, 209–211.

[177] Choudary, B. M.; Sridhar, C.; Kantam, M. L.; Venkanna, G. T.; Sreedhar, B.; *J. Am. Chem. Soc.* **2005**, 127, 9948–9949.

[178] Kang, S.-K.; Kim, J.-S.; Choi, S.-C.; *J. Org. Chem.* **1997**, 62, 4208–4209.

[179] Kang, S.-K.; Kim, W.-Y.; Lee, Y.-T.; Ahn, S.-K.; Kim, J.-C.; *Tetrahedron Lett.* **1998**, 39, 2131–2132.

[180] Bandaru, M.; Sabbavarpu, N. M.; Katla, R.; Yadavalli, V. D. N.; *Chem. Lett.* **2010**, 39, 1149–1151.

[181] Liu, T.-J.; Yi, C.-L.; Chan, C.-C.; Lee, C.-F.; *Chem. Asian J.* **2013**, 8, 1029–1034.

[182] Kuninobu, Y.; Nishina, Y.; Takeuchi, T.; Takai, K.; *Angew. Chem. Int. Ed.* **2007**, 46, 6518–6520.

[183] Kuninobu, Y.; Kawata, A.; Nishi, M.; Takata, H.; Takai, K.; *Chem. Commun.* **2008**, 6360–6362.

[184] Kuninobu, Y.; Nishi, M.; Kawata, A.; Takata, H.; Hanatani, Y.; Yudha S., S.; Iwai, A.; Takai, K.; *J. Org. Chem.* **2010**, 75, 334–341.

[185] Tsuji, H.; Yamagata, K.-i.; Fujimoto, T.; Nakamura, E.; *J. Am. Chem. Soc.* **2008**, 130, 7792–7793.

[186] Yoshikai, N.; Zhang, S.-L.; Yamagata, K.-i.; Tsuji, H.; Nakamura, E.; *J. Am. Chem. Soc.* **2009**, 131, 4099–4109.

[187] Nakamura, M.; Endo, K.; Nakamura, E.; *J. Am. Chem. Soc.* **2003**, 125, 13002–13003. Endo, K.; Hatakeyama, T.; Nakamura, M.; Nakamura, E.; *J. Am. Chem. Soc.* **2007**, 129, 5264–5271.

[188] Zhou, B.; Chen, H.; Wang, C.; *J. Am. Chem. Soc.* **2013**, 135, 1264–1267.

[189] Leadbeater, N. E.; Marco, M.; *J. Org. Chem.* **2003**, 68, 5660–5667.

[190] Arvela, R. K.; Leadbeater, N. E.; Sangi, M. S.; Williams, V. A.; Granados, P.; Singer, R. D.; *J. Org. Chem.* **2005**, 70, 161–168.

[191] de Vries, A. H. M.; Mulders, J. M. C. A.; Mommers, J. H. M; Henderickx, H. J. W.; de Vries, J. G.; *Org. Lett.* **2003**, 5, 3285–3288.

[192] Shirakawa, E.; Watabe, R.; Murakami, T.; Hayashi, T.; *Chem. Commun.* **2013**, 49, 5219–5221.

[193] Susuki, T.; Tsuji, J.; *J. Org. Chem.* **1970**, 35, 9, 2982–2986. Shvo, Y.; Green, R.; *J. Organomet. Chem.* **2003**, 675, 77–83.

[194] Smith, D. M.; Pulling, M. E.; Norton, J. R.; *J. Am. Chem. Soc.* **2007**, 129, 770–771.

[195] Luo, Y.-R.; *Comprehensive Handbook of Chemical Bond Energies*, **2007**, CRC Press.

[196] Rousseau, G.; Robin, S.; in *Modern Heterocyclic Chemistry*; Eds. Alvarez-Builla, J.; Vaquero, J. J.; Barluenga, J.; Wiley-VCH Verlag GmbH & Co. KGaA.; **2011**, chapter 3, 163–268.

[197] Chowdhury, S.; Roy, S.; *Tetrahedron lett.* **1996**, 37, 2623–2624.

[198] Huang, L.; Cheng, K.; Yao, B.; Zhao, J.; Zhang, Y.; *Synthesis* **2009**, 3504–3510.

[199] Guérinot, A.; Serra-Muns, A.; Gnamm, C.; Bensoussan, C.; Reymond, S.; Cossy, J.; *Org. Lett.* **2010**, 12, 1808–1811.

[200] Liu, Z.-Q.; Sun, L.; Wang, J.-G.; Han, J.; Zhao, Y.-K.; Zhou, B.; *Org. Lett.* **2009**, 11, 1437–1439.

[201] McConville, M.; Saidi, O.; Blacker, J.; Xiao, J.; *J. Org. Chem.* **2008**, 74, 2692–2698.

[202] Tan, J.; Zhang, Z.; Wang, Z.; *Org. Biomol. Chem.* **2003**, 6, 1344–1348.